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Insights into the impact of ACEI/ARBs on COVID-19 prognosis: A multi-state model of nationwide hospital surveillance data

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Keywords

Angiotensin-converting enzyme inhibitors (ACEI); Angiotensin-receptor blockers (ARBs); COVID-19; comorbidities; multi-state model.

Abstract

Objectives: The widespread use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in patients by chronic patients raised early concerns on the potential exacerbation of COVID-19 severity and fatality. A number of conflicting studies have used standard methods that may lead to biased estimates when analyzing hospital data because of the presence of competing events and time-dependent complexity. We investigated the effect of ACEI/ARBs use COVID-19 disease outcomes using time-to-event data in a multi-state setting to account for competing events and minimize bias.

Setting: Nationwide surveillance data from 119 Belgian hospitals.

Participants: Medical records of 10,866 patients hospitalised from March 14 to June 14, 2020 with a confirmed SARS-CoV-19 infection and information about ACEI/ARBs use.

Primary outcome measure: Multi-state, multivariate Cox-Markov models were used to estimate the hazards of patients transitioning through health states from admission to discharge or death, along with transition probabilities calculated by combining the baseline cumulative hazard and regression coefficients.

Results: After accounting for potential confounders no evidence was found of a detrimental effect of ACEI/ARBs use on admission to intensive care (ICU) or on in-hospital death. Contrastingly, ACEI/ARBs use was associated with a modest positive effect on recovery (HR 1.07 [95%CI 1.01-1.13], p=0.027) and reduced fatality (0.83, 0.75-0.93, p=0.001). For patients needing ICU admission, no evidence of an association between ACEI/ARBs use and recovery (1.16, 0.97-1.38, p=0.098) or in-hospital death during ICU (0.91, 0.73-1.12, p=0.381) was observed. Male gender and older age were significantly associated with higher risk of ICU admission or death. Chronic cardiometabolic comorbidities were also associated with less recovery.

Conclusions: For the first time, a multistate model was used to address magnitude and direction of the effect of ACEI/ARBs use on COVID-19 progression. By minimizing bias, this study provided robust indication a protective, albeit modest, effect on recovery and survival.

Keywords: Angiotensin-converting enzyme inhibitors (ACEI); Angiotensin-receptor blockers (ARBs); COVID-19; comorbidities; multi-state model.

Strengths and limitations of this study

- The study uses nationwide hospital surveillance data, and includes all general hospitals in Belgium.
- The use of a comprehensive database, but more so the utilization of models that adequately fitting to time-to-event hospital data with mutually exclusive health states results in less probability of introducing biases and are crucial for correct evidence-based information for decision making.
- Only transfer to intensive care was linked to a calendar date and was therefore the only event which could be used as a proxy for severe disease state in our time-dependent model, indicating that our estimates might represent more a critical state of the patient.
- Our analysis provided robust estimation a protective effect on ACEI/ARBs in recovery and survival of hospitalized COViV-19 patients.

1. BACKGROUND

COVID-19 virus infection is likely to cause severe disease among older individuals, men and patients with chronic respiratory or cardiometabolic conditions such as cardiovascular disease (CVD), hypertension (HTN) and diabetes (DM) [1-3]. Also, common risk factors for chronic conditions, such as smoking and particularly obesity, have been identified as key predictors of hospitalization and critical illness, even in young adults with no underlying conditions [4,5]. While the pathogenesis of certain chronic diseases predisposes to severe COVID-19 outcomes, common medications might also increase this risk because of the interaction between SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2)[6], an enzyme that physiologically counters the renin-angiotensin-aldosterone system (RAAS) activation.

SARS-CoV-2 binds to target cells using the angiotensin-converting enzyme 2 (ACE2) in cell membranes [6], a component of the RAAS, that can degrade angiotensin II to attenuate its subsequent physiological action (vasoconstriction). Modulation of RAAS is a frequent mode of action of antihypertensive and hypoglycemic drugs. HTN is commonly treated with ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) which results in an upregulation of ACE2. Expression of ACE2 is substantially increased in patients with HTN or type 1 or 2 DM, who are treated with ACEI or angiotensin receptor blockers (ARBs), and this may explain the higher risk for severe or fatal covid-19 infection among this patients. This information suggests that ACE2 expression is increased in hypertensive and diabetic patients treated with ACEI and ARBs (and potentially other commonly used drugs for the management of chronic conditions) worsening the prognosis of COVID-19 infection. This raised immediate concerns during the first phases of the outbreak of SARS-CoV-2 pandemic because of the widespread used RAAS inhibitors, specifically ACEI or ARBs among chronic, mostly hypertensive or diabetic, patients [7]. As patients with chronic comorbidities were also identified as more vulnerable to severe COVID-19 disease, it is necessary to understand whether part of this vulnerability could be

attributed to the use of ACEI/ARBs and to evaluate the risk of discontinuing this otherwise essential, first-line therapy, for hypertensive and diabetic patients.

To date, a number of studies addressing the potential effect of ACEI and ARBs on the prognosis of COVID-19 have been reported, mostly supporting the absence of harmful effects of these drugs on COVID-19 prognosis [8-10]. In these studies, a wide range of statistical methods have been used to test this hypothesis, including comparison of proportions, percentage points, logistic regression, or time-to-event analysis and Cox models. The use of standard methods for these particular analyses can easily lead to biased estimates, in particular when analyzing hospital data because of the presence of competing events, such as death and recovery, and the time-dependency of these competing events [11]. As such, the analysis of the association of ACEI/ARBs on the progression of COVID-19 or related mortality requires the assessment of competing risks/events. Analyzing time-to-event data in a multi-state setting would better fit the true progression of COVID-19 in hospitalized patients, as shown by two studies using the multi-state-approach in a COVID-19 context [12,13]. Multi-state models allow for studying clinically competing events (discharged alive vs deceased), as well as disease progression (in terms of hospital stay duration, transfer to Intensive Care Unit (ICU), treatment received), simultaneously over time. This multi-state model framework ensures avoiding bias that stems from censoring patients (informative censoring bias), as well as circumvents time-dependent bias by treating disease progression as a transient state that might influence the probability of experiencing a certain future outcome depending on patient's risk factors. While accounting for these biases, we revisited the the hypothesis of the potential effect of ACEI/ARBs use in patient's prognosis during hospitalization using a competing risk multi-state model and nationwide hospital surveillance data on COVID-19 patients in Belgium.

2. PATIENTS AND METHODS

2.1. Data sources

All methods were carried out in accordance with relevant guidelines and regulations. Nationwide hospital surveillance data on COVID-19 patients in Belgium are routinely gathered by Sciensano, the Belgian Institute of Public Health, which is legally entitled institution for surveillance of infectious diseases in Belgium (Royal Decree of 21/03/2018). Retrieving informed consent was determined as a disproportional load on the hospital resources in the crisis situation. An information letter was given to the patients at the time of discharge which contained an explanation of their rights concerning the data that was gathered by Sciensano. The COVID-19 hospital surveillance was authorised by an independent administrative authority protecting privacy and personal data and was approved by the ethical committee of Ghent University Hospital (BC-07507). Details on the Belgian COVID-19 hospital surveillance system have been previously published [14]. The system cover 119 hospitals in Belgium, who report standardized information on hospitalized COVID-19 patients collected through a structured questionnaire at hospital admission and discharge. An anonymized subset of data from Sciensano was shared with the Institute of Tropical Medicine through a secured data transfer platform applying data encryption. Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Tropical Medicine after revision of the research protocol num. 1393/20, 02/05/2020.

Variables collected at admission include the date of hospital admission, reason for hospitalization, symptoms, clinical signs, treatment with ACEI or ARBs, and demographic information such as age, gender, and the presence of chronic comorbidities. Information recorded at discharge includes laboratory values, details on COVID-19 specific treatments during hospital stay, date of discharge, health status at discharge, and measures on the severity of the disease such as the need for transfer to ICU, invasive ventilation support and/or oxygenation by extracorporeal membrane oxygenation (ECMO), and the development of a bacterial and/or fungal superinfection, pneumonia, and/or acute respiratory distress syndrome (ARDS). Dates for these severe events were only available for ICU transfer.

2.2. Study population

Adult COVID-19 patients with a SARS-CoV-19 infection confirmed by polymerase chain reaction (PCR), and/or suggestive imaging alterations on chest CT combined with typical clinical presentation, at admission or while hospitalized in Belgium from March 14 to June 14, 2020 were considered as COVID-19 patients (n=16,341). Of these, patients with completed questionnaires both on admission and discharge (12,109 patients, 74.1%) were selected. Information on patients admitted to hospitals before March 1 2020 (270, 1.65%) for reasons other than COVID-19 and infected while hospitalized was also removed. Furthermore, patients with implausible admission dates were removed, including: Date of discharge before date of admission (42 patients, 0.25%); Date of ICU transfer preceding date of admission (31 patients, 0.19%); Date of discharge before date of ICU transfer (2 patients, 0.01%); Date of discharge preceding the date of ICU discharge if the difference was more than 1 day (47 patients, 0.28%). The final dataset for descpritive analyses included information on 11717 COVID-19 patients. For the multivariate multi-state model, patients with unknown use of ACE/ARBs (718 patients, 6.12%) were also excluded, along with those missing information on gender (118 patients, 0.72%) or unknown transfer to ICU (15, 0.09%). The final dataset for the multi-state model contained information from 103 hospitals in Belgium and 10,866 COVID-19 patients, including 539 patients (5%) that were admitted directly to ICU.

2.3. Study outcomes

Patients were considered to have recovered when their status at discharge was recorded as “cured” or “other”. In the latter case, it was assumed they were allowed to recover at home, revalidation center or nursing home. Patients were considered to have an in-hospital death when their status at discharge was recorded as “death”. Patients were considered lost to follow up when their status at discharge was recorded as “unknown” or when they were transferred to another hospital (status at discharge = “transfer to another hospital”), as no further information was available. Severe COVID-19 was captured in the database as an illness that: required ECMO, or artificial ventilation, experienced ARDS, pneumonia, bacterial and/or fungal co-infection, or required transfer to or

treament at ICU. Among these, event date was only available for transfer to ICU, and only this variable could therefore be selected for the models as time-defined severity outcome. Based on this, time to severe illness was defined as the time passed from hospital admission to date of transfer to ICU. Length of hospital stay was defined as date from hospital admission to the date of hospital discharge (either recovery, in-hospital death, or lost to follow-up).

2.4. Information on ACEI/ARBs and conditions related to COVID-19 prognosis

A dedicated section in the admission dataset covered the use of ACEI, ARBs or both, without specification of the specific drug. The admission database contained information on the following factors associated with COVID-19[15]. Demographics (age and gender), risk factors (current smoking, high blood pressure (HBP), and obesity), prevalent comorbidities (DM, chronic renal disease, CVD, chronic lung disease, chronic liver disease, malignant solid neoplasms, hematological cancers, and immunosuppression). Smoking status was only available for 53% of the patients. Obesity presented a large number of missing values (33.2%) because this variable was only recorded after April 3, 2020. Similarly, there was also number of missing values for cognitive issues (5.7%) as this variable was only recorded after March 23, 2020.

2.5. Patient and public involvement

As a secondary data analysis of COVID-19 surveillance data this study did not involve patients or the public in the design, conduct or dissemination plans.

3. STATISTICAL MODEL

Patient's characteristics at admission, during ICU, and discharge were visualized on histograms and summarized as means and standard deviation and counts and percentage for continuous and categorical variables, respectively. Descriptive analyses were provided for patients overall and stratified by ACEI/ARBs use, including unknown use.

To study the impact of ACEI/ARBs on COVID-19 progression on a multivariate multi-state model, a first model for identiying confounders was used. A backwards stepwise logistic regression with

ACEI/ARBs use as dependent variable and including factors and conditions previously associated with COVID-19 outcomes present in the database [16,17], was used to inform the selection of potential confounders based on Akaike's information criterion (AIC). The variables used in the variable selection model were: gender, age, HBP, CVD, DM, obesity, chronic renal disease, chronic liver disease, chronic lung disease, solid malignant neoplasms, hematological cancers, immunodepression, and cognitive impairment. Two models were used depending on the availability of data, a first model (model 1) excluding variables collected at a later date (obesity, and cognitive issues) and using a full dataset (N=10,866), and a complete case analysis (model 2) excluding patients with missing data for obesity and cognitive issues (N=7,303).

We devised a multi-state model reflecting the progression of patients from admission to discharge accounting for the patient's characteristics identified to be potential confounders, and introducing ACEI/ABRs use as dependent variable. The model starts with one initial state (hospitalization), a potential (transient) state defined as ICU transfer (as a proxy for severe COVID-19 disease, as only ICU transfer had an associated time in the database) and two absorbing states (in-hospital death, and recovery). The multi-state model is characterized by transition hazards between the states; defined as the instantaneous risk for moving from one state to another. The transitions hazards are used to calculate transition probabilities, as the conditional probabilities of experiencing future outcomes, given the history and a particular set of prognostic factors (model covariates) for a given patient. The four-state model thereby comprised five possible patient's transitions; 1) hospitalization to ICU, 2) hospitalization to recovery, 3) hospitalization to in-hospital death, 4) ICU to recovery, and 5) ICU to in-hospital death, as presented in Figure 1. A Cox-Markov model for the regression on the transition specific hazards was fitted using the *coxph* and *msfit* functions in R *survival* package[18]. This approach is equivalent of constructing five separate Cox regression models, one for each transition hazard. The cumulative baseline transition hazard (all covariate values equal to the reference value) was estimated by the Breslow estimator with the Aalen estimator of variance [19]. We integrated these separate Cox models in a multi-state framework studying different outcomes simultaneously and allowing the

calculation of transition probabilities. The transition probabilities were then estimated by combining the baseline cumulative hazard and regression coefficients. Using R, *mstate* package was used with *msfit* function to obtain cumulative (baseline) transition hazards and the function *probtrans* to obtain the transition probabilities[20]. Estimates obtained from the Cox-Markov models are displayed in a table and significance is established at the 5% significance level. Cumulative (baseline) transition hazard plots and transition probability plots were also generated for visual aid. In a setting with covariates, a regression model for the transition specific hazards was used, whereby the covariates may help to explain the difference in transition hazards. Model diagnostics were performed to check model assumptions of proportional hazards, linearity, and interactions. Assumptions to the Markov model were assessed by including time from hospital admission to ICU transfer in the model for transition 4 and transition 5. A relaxation of the Markov assumption was also explored in the analysis.

4. RESULTS

4.1. Descriptive analysis

From the 11,717 patients available for this analysis, almost of all them (94.2%) presented symptoms or clinical signs compatible with COVID-19 at admission (Supplemental Table 1). Most frequent symptoms were fever (61.3%) and cough (53.2%), and most frequent signs were abnormal pulmonary imaging (63.1%) compatible with viral pneumonia, abnormal auscultation (44.8%), and dyspnea (42.4%). On admission, 15.1% of patients had a record of taking ACEI, and 8.5% ARBs, with only 0.4% taking both ACEI and ARBs. For the purpose of this analysis these patients were merged as ACEI/ARBs users. The majority of patients (69.9%) were nonusers of ACEI/ARBs versus 23.9% of users, and only for a small proportion (6.1%) of patients the use of ACEI/ARBs was unknown (Table 1). No difference was seen in the frequency of signs and symptoms reported according to ACEI/ARBs use (Supplemental Table 1). Patients using ACEI/ARBs were markedly older (median [IQR] age 76 [65-84] years) than non-users (67 [53-81] while no sex-differences were observed. As expected, ACEI/ARBs users presented more frequently (74.4%) HBP than non-users (39.2%), as well as chronic lung disease

(16.8% vs 14.4%), chronic renal disease (19.3% vs 11.1%), DM (33.3% vs 18.1%), and particularly CVD (53.1% vs 28.4%). Among ACEI/ABRs users with 15.1% of them suffering multiple comorbidities (HBP, DM and CVD) versus 4.9% in non-users (Table 1). During hospital stay, over 80% of COVID-19 patients suffered one severe episode of either pneumonia, superinfection, ARDS, or mechanical ventilation, and 25.9% of patients had two or more severe episodes (Table 2). The most common manifestation of COVID-19 severity was pneumonia (79.1%), followed by other infections (19.4%), ARDS (12.7%), and artificial ventilation (7.6%). Frequency of severe conditions was almost the same for both ACEI/ARBs users and non-users (27.8% versus 25.4%). Of all admitted patients, 1,518 (13.0%) were transferred to ICU, mostly those with severe pneumonia (93.7%), or in need of artificial ventilation (58.0%), and for a mean duration of 11.5 ± 10.7 days. Transfer to ICU was marginally more frequent among ACEI/ARBs users (15.1% versus 12.1%). Almost 78% of the patients admitted to Belgian hospitals recovered from COVID-19, either in the hospital (51.2%) or at home or revalidation centre or nursing home (26.4%) after an average 12.6 ± 10.9 days in the hospital. Only 2% was lost to follow-up (transferred to another health care provider or unknown status at discharge).

4.2. Multi-state model

A multivariate state-arrival extended Cox-Markov model was used to study the potentially different progression of COVID-19 patients through health states during hospitalization according to the use of ACEI/ARBs. Possible transitions, and number of patients in each health state are represented in Figure 1. The selection of variables for adjusting the models were based on backwards stepwise logistic regression of ACEI/ARBs use as a function of potential confounding factors associated with COVID-19 recorded at admission (Table 2 Supplemental). A first model (model 1) using all available patients, identified five variables associated with the use of ACEI/ARBs and COVID-19: male gender (OR 1.33, 95%CI 1.21-1.47), older age (1.01, 1.01- 1.02 per 1-year increase), and prevalent CVD (1.71, 1.55 -1.90), diabetes (1.38, 1.24-1.54), and HBP (5.65, 5.10-6.27). Additionally, a second model (model 2) was used in sensitivity analysis including additional covariates (prevalent obesity and cognitive impairment) that were only available in a subset (62%) of patients (Table 2 Supplemental). Because very few patients

were asymptomatic on admission it was deemed unnecessary to adjust the regression models for severity of disease at admission. For 16 patients (0.1%) it was unknown whether they were transferred to ICU. These patients are therefore excluded from the multistate Cox-Markov regression analysis.

Plots for the cumulative hazard and transition probability between health states considering ACEI/ARBs use were obtained by setting all model covariates to reference values (female gender, no CVD, no HBP, and no DM), and median (70 years) age Figure 2. When looking at the cumulative hazard for the five possible transitions (Figure 2A), the hazard for recovery was markedly greater than that of in-hospital death. In comparison with the other cumulative hazards, the hazard for transfer to ICU was substantially smaller, representative of most COVID-19 patients not needing intensive care, or not meeting criteria for admission (for instance after evaluation of frailty, and chance of survival). Transfer to ICU was associated with increased hazard for in-hospital death and reduced hazard for recovery. The use of ACEI/ARBs was associated with a modest but significant effect on the hazard of transition 2 (more recovery) and 3 (less in-hospital death), from admission. The use of ACEI/ARBs was not observed to be associated with transfer to ICU (transition 1), nor with recovery (transition 4) or in-hospital death (transition 5) after ICU. Overall, the probability of being transferred to ICU was for most patients less than that of recovery (Figure 2B). However, those needing ICU had a reduced probability of recovery and greater probability to decease in the hospital than those patients not transferred to ICU (Figure 2C).

The estimates for the transition hazards for ACEI/ARBs use accounting for identified confounding in the potential association woth COVID-19 severity/fatality are presented in Table 3. In multivariate models, the use of ACE/ARBs (HR 1.07, 95%CI 1.01-1.13) was associated with more recovery, and less death (0.83, 0.75-0.93). Even though there was a significant association between ACEI/ARBs use the hazard of more recovery (transition 2), and less in-hospital death (transition 3) this effect is modest, especially when inspecting state-occupation probabilities (Figure 1 Supplemental). In respect to the adjusting variables (Table 3 Supplemental), male gender and HBP were associated with transfer to ICU (severity), and older age also influenced this transition. Similarly, male gender, and

older age, as well as prevalent CVD, HBP or DM were associated with less recovery. Similar to transfer to ICU, fatal progression was associated with male gender and age, as well as with prevalent CVD. No other comorbidity included in this model (i.e. associated with ACEI/ARBs use) appeared to be associated with fatality. For severe patients (transferred to ICU) recovery or death depended mostly on age, albeit fatal COVID-19 associated with the presence of DM, and a lengthier period between admission and ICU were significant associated with less recovery after ICU (Table 3 Supplemental). The impact of further adjustment for variables identified during confounder selection (obesity and cognitive issues) in the state transition of COVID-19 patients during hospitalization, resulted in loss of more than half of all patients due to missing values (Table 1). While estimated hazards for previous factors remained similar, the presence of cognitive issues was statistically significantly associated with transitions 1, 2, and 3 (*i.e.* less transfer to ICU, less recovery, and more in-hospital death), and obesity was strongly and statistically significantly associated with transition 1 only (more transfer to ICU). In this complete-case model, after additional adjustment for obesity and cognitive issues, the HR for ACEI/ABRs use for transition 2 (admission to recovery) is not anymore significant probably due to a decreased statistical power, since the point estimates remained similar.

5. DISCUSSION

In this study, a competing risk multistate model has been developed for the first time to address the magnitude and direction of the effect of ACEI/ARBs use in COVID-19 prognosis. Our analyses indicate a protective effect of ACEI/ARBs use, with increase recovery and survival, once important confounding factors such as age, particularly 70 and over, and male gender are accounted for. Chronic comorbidities such as CVD, HBP, and DM are also associated with less recovery in this model setting. Although there is a protective effect of ACEI/ARBs use on COVID-19 in-hospital death and more recovery, this effect is modest, especially when looking at the state-occupation probabilities. In our model, once the patient progresses to a severe state, no effect of ACEI/ARBs use was observed in the transition probabilities to recovery or in-hospital death; only older age and prevalent DM,

remained significant covariates in or model, arguably because of the smaller sample size (transfer to ICU occurred only for 13% of patients). Previous studies using the same data source identified other comorbidities as independent risk factors for COVID-19 severity/death in ICU patients, including chronic pulmonary disease, chronic renald disease, and immunosuppression [21]. Although we accounted for these factors in our model selection, they were not selected as they are not considered to be related to the use of ACEI/ARBs but may nonetheless be independent risk factors for severity.

Because of the high clinical relevance, there have been numerous reports on studies of the potential association between ACEI/ARBs and (worse) prognosis of COVID-19. Early studies of smaller sample size and mostly descriptive design pointed to either no association or moderately lower rates of severe disease among ACEI/ARBs users [22-27]. Further retrospective analysis involving larger patient samples generally reported a lack of association [8]. A population-based study in Italy's Lombardy region involving 6,272 cases identified across the Regional Health Service and matched 1:5 to population-based control, found no association between the use of ACEI (adjusted OR 0.91, [95%CI 0.69-1.21]) or ARBs (adjusted OR 0.83, [95%CI 0.63-1.10]) and severe/fatal COVID-19 [28]. Similarly, a case-control study in the Spanish region of Madrid with data on 1,139 hospitalized cases matched 1:10 to population controls found no association (adjusted OR 0.94, [95%CI 0.77-1.15]) of ACEI/ARBs use and severe or fatal disease [29]. Analyzing data from all patients in the New York University Langone Health electronic health record who had COVID-19 test results (12,594 patients), neither increased likelihood of a positive test nor severe disease was observed for patients using ACEI/ARBs (or any other RAAS medication) using propensity score matching [30]. In a nationwide study in Korea using claim records of 66,793 individuals tested for COVID-19, the use of ACEI/ARBs was not associated with a higher risk of mortality (adjusted OR 0.88, [95%CI 0.53-1.44]) [31]. Similarly, a large retrospective analysis of an Italian registry cohort including 43,000 patients concluded that neither ACEI (adjusted HR 0.97, [95%CI 0.89-1.06]) or ARB (adjusted HR 0.98, [95% CI 0.89-1.06]) use was associated with either an increased or decreased risk of all-cause mortality [32]. A multicenter study with 1,128 hypertensive patients, and using mixed-effect Cox models (site as a random effect, and model adjusted for age, gender, comorbidities,

and in-hospital medications) reported a lower risk for all-cause mortality in the ACEI/ARB patients versus the non-ACEI/ARB group (adjusted HR 0.42, [95%CI 0.19-0.92]), and further compared with the use of other antihypertensive drugs, (adjusted HR 0.30, [95%CI, 0.12-0.70]) [33]. Previous studies using Cox models reported also a reduced mortality risk for patients using ACEI/ARBs [33,34]. In others, albeit not statistically significant, estimates were very similar to the ones reported in our study for mortality (adjusted HR 0.83, [95%CI 0.67-1.03]) and for severe disease (adjusted HR 1.15, [95%CI 0.95-1.41]) [35]. Similarly, but outside of the hospital setting, studies with data from general practitioners in England, found a strong association of ACEI/ARBs use and a reduced risk of COVID-19 disease (HR 0.63, [95%CI 0.59-0.67]) albeit not severity (HR 1.02, [95%CI 0.83-1.25]), and marked interactions with ethnicity with higher risks observed for Black Africans compared to Whites[36]. Variations between different ethnic groups raise the possibility of specific effects of ACEI/ARBs on COVID-19 disease susceptibility and severity which deserves further study. Three review papers on the topic have concluded there is either no difference or a reduced risk when looking at mortality and/or severe disease [8,37,38]. Our study builds on these previous reports where other standard statistical models were used for analysis, with potential introduction of biases [11]. Integrating standard cox models into a multi-state framework allows the study of separate outcomes simultaneously and allows the calculation of the transition probabilities, adding a layer of interpretation. We used a time-to-event analysis considering competing risks to account appropriately for censoring [39], thereby robustly showing a modest, yet significant, positive effect of ACEI/ARBs use in recovery and survival of hospitalized COVID-19 patients accounting for confounding factors.

Our study uses nationwide hospital surveillance data, with mandatory participation, and includes all general hospitals (including university hospitals) in Belgium, both those managed by a public authority and privately managed are represented. The surveillance does not cover psychiatric hospitals or specialist hospitals [14]. The use of comprehensive datasets, but more so the utilization of models adequately fitting to time-to-event hospital data with mutually exclusive health states results in less probability of introducing biases and are crucial for correct evidence-based information for

decision making. Our study makes some assumptions, and unknowns such as the lack of information on ACEI/ARBs exact indication and whether their use was continued after admission. Our models are not adjusted for severity at baseline since we reasoned that hospital admission was already an indicator of severe disease and 94% of patients had symptoms compatible with COVID-19 diagnosis at baseline. Further, even though other events potentially indicating severity (ECMO, ARDS, pneumonia, bacterial and/or fungal co-infection) were available in the database, only transfer to ICU was linked to a calendar date and was therefore the only event which could be used as a proxy for severe health state in our time-dependent model, indicating that our estimates might represent more a critical state of the patient. In addition, admission to intensive care is not solely based on the clinical status of the patient, but also on other criteria such as frailty. Also, ICU admission criteria might have been more restrictive in the peak period of the epidemic whilst certain ICU were overloaded. Because the surveillance data is limited to the most important variables, we cannot discard the possibility of some degree of residual confounding in our results. An important limitation of our main analysis is the impossibility of adjusting our models for smoking status, obesity and cognitive issues at baseline. Using available smoking information was not considered due to the excessive number of missing values, and the lack of information of the reason for the incomplete data. We used however data on obesity and cognitive issues, which collection was introduced later, in a complete case analysis to confirm the results obtained in the main model. Nevertheless, these analyses on a reduced sample of patients should be interpreted with caution as a time effect is likely present because of the late data collection. Finally, our analyses are based on patient's medical files and rely on how clinicians reported clinical observations and anamnesis which might vary across hospitals, and are representative of the first so called wave of the epidemic in Belgium, and associations might differ in subsequent studies.

6. CONCLUSIONS

After adjustment for important confounders there is modest, yet significant, positive effect of ACEI/ARBs use on recovery and survival of hospitalized COVID-19 patients, without affecting admission to intensive care. This supports the use of ACEI/ARB in those patients who need them, also when needing hospitalization from COVID-19. These findings are based on an analytical model that adequately fits hospital data, where patients progress across different, competing, health states providing a more complete and acurate view of the research question within a reduced risk of bias framework. Integrating standard cox models into a multi-state framework allows the study of separate outcomes simultaneously and allows the calculation of the transition probabilities, adding a layer of interpretation. Multi-state models should be favoured over separate survival analysis when competing risks are present, and traditional methods such as logit functions should be discouraged when time-to-event is available.

Contributorship statement

JLP, MvdS, MAW, DV conceptualized the study. DV performed data curation and provided data. JLP, EG, EM, DS developed methodology, and performed analysis. JLP supervised the study, and drafted the manuscript. All authors have critically reviewed, commented, and approved the manuscript before submission.

Competing interest

The authors declare that they have no competing interests.

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Data availability

The data that support the findings of this study are available from Sciensano but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Sciensano.

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AUTHOR CONTRIBUTIONS

JLP, MvdS, MAW, DV conceptualized the study. DV performed data curation and provided data. JLP, EG, EM, DS developed methodology, and performed analysis. JLP supervised the study, and drafted the manuscript. All authors have critically reviewed, commented, and approved the manuscript before submission.

DATA AVAILABILITY

The data that support the findings of this study are available from Sciensano but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Sciensano.

ETHICS DECLARATION

Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Tropical Medicine after revision of the research protocol (num. 1393/20, 02/05/2020).

FIGURE TITLES

Figure 1. Schematic representation of the competing risk multi-state model and transition event matrix (number (%) patients in each transition.

Figure 2. Plots for cumulative transition hazards (A), and state transition probabilities (B), and transition probabilities after transfer to intensive care (C) in a multi-state competing risk model considering ACEI/ARBs use (dashed line) versus no use (solid line).

Figure 1 Supplemental. Staked probability plot of the state-occupation probabilities in a multi-state competing risk model considering ACEI/ARBs use (A) versus no use (B).

Table 1. COVID-19 patient's characteristics at hospital admission according to ACEI/ARBs use

	Total	ACEI/ARBs		
	(n = 11717)	No use (n = 8189, 69.9%)	Use (n = 2810, 23.9%)	Unknown use (n = 718, 6.1%)
Demographics				
Age (years) (mean (SD))	67.82 (17.17)	65.70 (17.90)	74.08 (12.85)	67.47 (17.50)
Equal or more than 70 years old (n, %)	6044 (51.6)	3791 (46.3)	1886 (67.1)	367 (51.1)
Sex (n, % males)	6154 (52.5)	4227 (51.6)	1562 (55.6)	365 (50.8)
Missing (n, %)	*129 (1.1)*	*93 (1.1)*	*25 (0.9)*	*11 (1.5)*
Risk factors				
Smokers (n, %)	606 (5.2)	440 (5.4)	142 (5.1)	24 (3.3)
Missing (n, %)	*5413 (46.2)*	*3667 (44.8))*	*1160 (41.3)*	*586 (81.6)*
Flu vaccination (n, %)	841 (7.2)	572 (7.0)	250 (8.9)	19 (2.6)
Missing (n, %)	*10076 (86.0)*	*7018 (85.7)*	*2374 (84.5)*	*684 (95.3)*
Obesity (n, %)*	782 (6.7)	478 (5.8)	271 (9.6)	33 (4.6)
Missing (n, %)	*3887 (33.2)*	*2735 (33.4)*	*870 (31.0)*	*282 (39.3)*
Chronic comorbidities				
HBP (n, %)	4593 (39.2)	2343 (28.6)	2090 (74.4)	160 (22.3)
DM (n, %)	2522 (21.5)	1486 (18.1)	936 (33.3)	100 (13.9)
Chronic renal disease (n, %)	1513 (12.9)	911 (11.1)	541 (19.3)	61 (8.5)
CVD (n, %)	3984 (34.0)	2326 (28.4)	1493 (53.1)	165 (23.0)
Chronic lung disease (n, %)	1731 (14.8)	1180 (14.4)	473 (16.8)	78 (10.9)
Cognitive impairment (n, %)**	1320 (11.3)	922 (11.3)	331 (11.8)	67 (9.3)
Missing (n, %)	*668 (5.7)*	*461 (5.6)*	*173 (6.2)*	*34 (4.7)*
Chronic neuro-muscular disease (n, %)	993 (8.5)	704 (8.6)	241 (8.6)	48 (6.7)
Solid malignant neoplasms (n, %)	990 (8.4)	697 (8.5)	261 (9.3)	32 (4.5)
Chronic liver disease (n, %)	301 (2.6)	210 (2.6)	79 (2.8)	12 (1.7)
Immunodepression (n, %)	297 (2.5)	224 (2.7)	64 (2.3)	9 (1.3)
Hematological cancers (n, %)	216 (1.8)	154 (1.9)	56 (2.0)	6 (0.8)
Combination of comorbidities				
None (n, %)	4760 (40.6)	4145 (50.6)	192 (6.8)	423 (58.9)
CVD & HBP (n, %)	1386 (11.8)	713 (8.7)	633 (22.5)	41 (5.7)
CVD & DM (n, %)	385 (3.3)	248 (3.0)	113 (4.0)	24 (3.3)
HBP & DM (n, %)	682 (5.8)	348 (4.2)	309 (11.0)	25 (3.5)
CVD & HBP & DM (n, %)	401 (50.6)	401 (4.9)	423 (15.1)	20 (2.8)

*ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers; CVD, cardiovascular disease; DM, diabetes mellitus; HBP, high blood pressure. *Values only collected after April 3, 2020. **Values only reported after March 23, 2020.*

Table 2. Frequency of severity events among COVID-19 patients during hospital stay and recorded outcomes at discharge according to ACEI/ARBs use at admission

		ACEI/ARBs		
	Total (n = 11717)	**No use (n = 8189, 69.9%)**	**Use (n = 2810, 23.9%)**	**Unknown use (n = 718, 6.1%)**
Severe conditions				
Pneumonia (n, %)	9265 (79.1)	6501 (79.4)	2260 (80.4)	504 (70.2)
Missing (n, %)	*532 (4.5)*	*372 (4.5)*	*73 (73)*	*87 (87)*
Superinfection (n, %)	2268 (19.4)	1548 (18.9)	589 (21.0)	131 (18.2)
Missing (n, %)	*1277 (10.9)*	*820 (10.0)*	*320 (11.4)*	*137 (19.1)*
ARDS (n, %)	1492 (12.7)	996 (12.2)	389 (13.8)	107 (14.9)
Missing (n, %)	*1047 (8.9)*	*671 (8.2)*	*263 (9.4)*	*113 (15.7)*
Mechanical ventilation (n, %)	893 (7.6)	571 (7.0)	249 (8.9)	73 (10.2)
Missing (n, %)	*627 (5.4)*	*383 (4.7)*	*170 (6.0)*	*74 (10.3)*
Number of severe conditions (n, %)				
None	2143 (18.3)	1492 (18.2)	465 (16.5)	186 (25.9)
One	6537 (55.8)	4620 (56.4)	1565 (55.7)	352 (49.0)
Two or more	3037 (25.9)	2077 (25.4)	780 (27.8)	180 (25.1)
Intensive care				
Transfer to ICU (n, %)	1518 (13.0)	990 (12.1)	425 (15.1)	103 (14.3)
Missing (n, %)	*16 (0.1)*	*16 (0.2)*	*0 (0)*	*0 (0)*
Transfer to ICU + pneumonia (n, %)	1423 (93.7)	932 (94.1)	395 (92.9)	96 (93.2)
Transfer to ICU + superinfection (n, %)	653 (43.0)	423 (42.7)	181 (42.6)	49 (47.6)
Transfer to ICU + ARDs (n, %)	831 (54.7)	547 (55.3)	224 (52.7)	60 (58.3)
Transfer to ICU + mechanical ventilation (n, %)	880 (58.0)	561 (56.7)	246 (57.9)	73 (70.9)
Length (days) of ICU stay (mean (SD))	11.5 (10.7)	11.415 (10.7)	11.3 (10.8)	12.9 (11.0)
Discharge status				
Recovered at discharge (n, %)	6003 (51.2)	4244 (51.8)	1378 (49.0)	381 (53.1)
Recovered at home (n, %)	3093 (26.4)	2201 (26.9)	722 (25.7)	170 (23.7)
In-hospital death (n, %)	2388 (20.4)	1574 (19.2)	622 (23.6)	152 (21.2)
Transferred (n, %)	201 (1.7)	149 (51.8)	44 (49.0)	8 (53.1)
Unknown (n, %)	32 (0.3)	21 (0.3)	4 (0.1)	7 (1.0)
Length (days) of hospital stay (mean (SD))	12.6 (10.9)	12.1 (10.5)	13.9 (11. 7)	12.2 (11.6

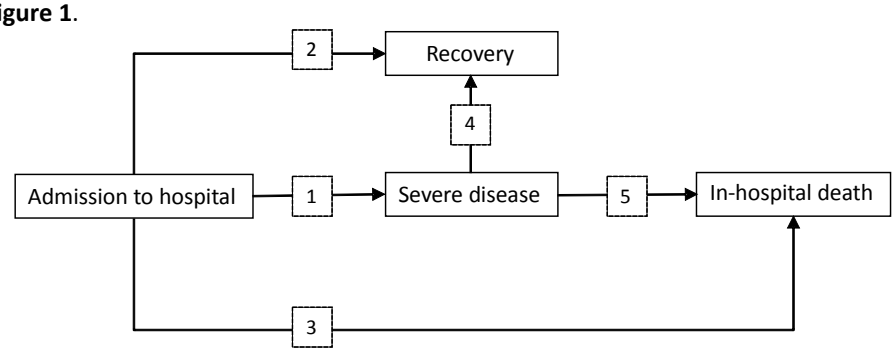
ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Table 3. State-arrival extended Cox-Markov multivariate model's transitions hazard ratios (HR, 95%CI) as a function of ACEI/ARBs

Transition		ACEI/ABRs use			
		Model 1	*p*-value	Model 2	*p*-value
1	**Admission → Severity**	1.15 (0.98, 1.36)	0.092	1.10 (0.88, 1.36)	0.409
2	**Admission → Recovery**	**1.07 (1.01, 1.13)**	0.027	1.05 (0.98, 1.13)	0.182
3	**Admission → Death**	**0.83 (0.75, 0.93)**	0.001	**0.80 (0.70, 0.91)**	0.001
4	**Severity → Recovery**	1.16 (0.97, 1.38)	0.098	1.16 (0.93, 1.45)	0.195
5	**Severity → Death**	0.91 (0.73, 1.13)	0.381	1.11 (0.83, 1.49)	0.485

ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers Model 1: Adjusted for gender, age (years), prevalent CVD, HBP, DM, and time (days) to severity; Model 2: Further by prevalent obesity, and cognitive issues.
Full output is presented in Table 3 supplemental.

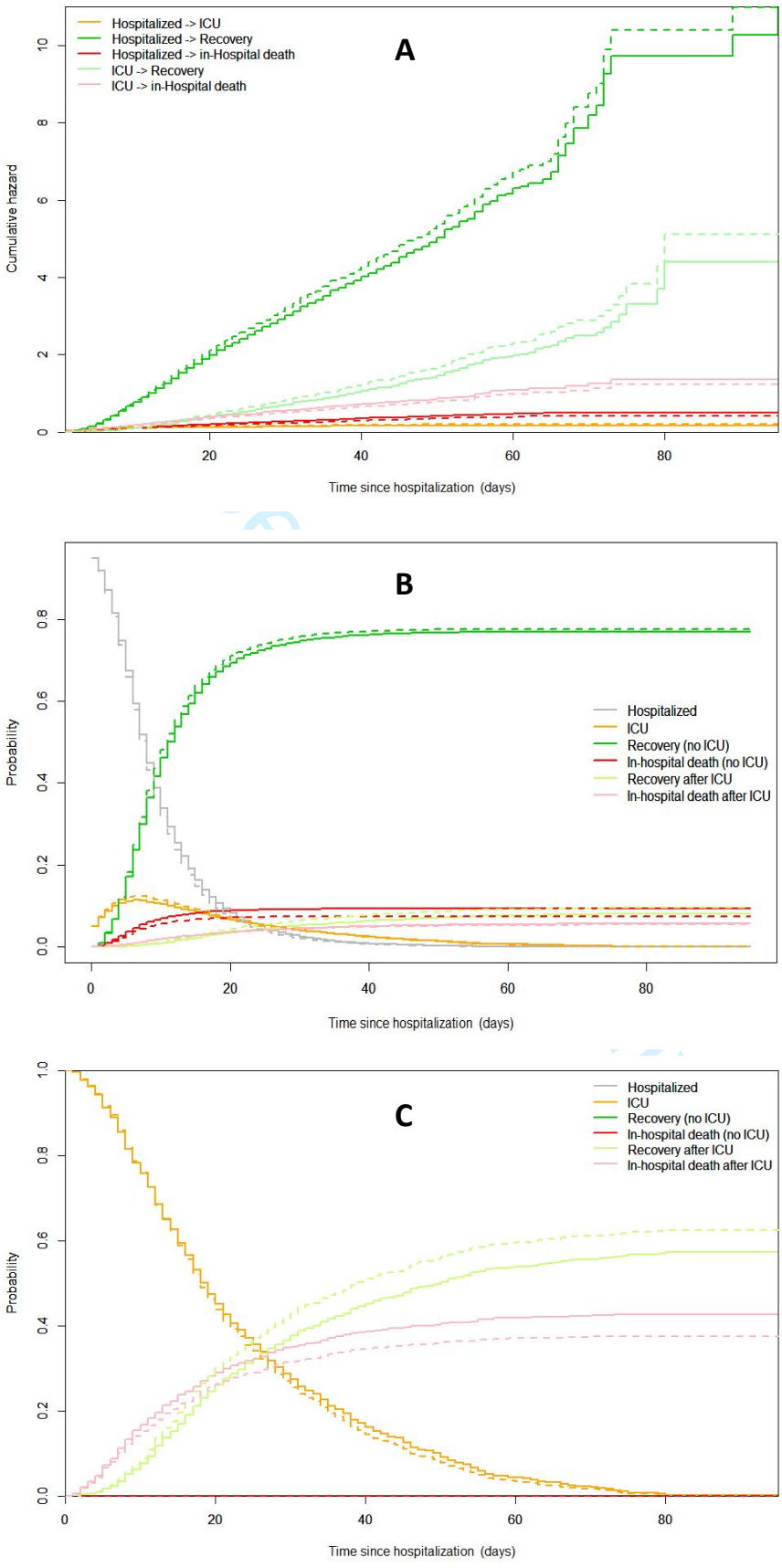
Figure 1.



From	To Admission	Severity	Recovery	Death	No event	Total
Admission	0	863 (8.4)[1]	7633 (73.9)[2]	1738 (16.8)[3]	93 (0.9)	10327
Severity	0	0	817 (58.3)[4]	468 (33.4)[5]	117 (8.3)	1402*
Recovery	0	0	0	0	8450 (100)	8450
Death	0	0	0	0	2206 (100)	2206

*Numbers in superscript represent transitions depicted in the figure.*539 patients were directly admitted to ICU*

Figure 2.



SUPPLEMENTAL MATERIAL

Table 1 Supplemental. Frequency of symptoms and clinical signs compatible with COVID-19 at hospital admission according to ACEI/ARBs use

	Total	ACEI/ARBs		
	(n = 11717)	No use (n = 8189, 69.9%)	Use (n = 2810, 23.9%)	Unknown use (n = 718, 6.1%)
Symptoms at admission	11039 (94.2)	7705 (94.1)	2673 (95.1)	661 (92.1)
Fever (n, %)	7187 (61.3)	5112 (62.4)	1653 (58.8)	422 (58.8)
Cough (n, %)	6231 (53.2)	4444 (54.3)	1438 (51.2)	349 (48.6)
Breathlessness (n, %)	5997 (51.2)	4194 (51.2)	1349 (52.0)	376 (47.6)
Weakness (n, %)	4672 (39.9)	3253 (39.7)	1153 (41.0)	266 (37.0)
Pain (n, %)	2622 (22.4)	1931 (23.6)	544 (19.4)	147 (20.5)
Diarrhea (n, %)	1673 (14.3)	1173 (14.3)	438 (15.6)	62 (8.6)
Nausea and vomiting (n, %)	1364 (11.6)	987 (12.1)	311 (11.1)	66 (9.2)
Headache (n, %)	1234 (10.5)	932 (11.4)	245 (8.7)	57 (7.9)
Irritability (n, %)	838 (7.2)	556 (6.8)	243 (8.6)	39 (5.4)
Throat pain (n, %)	700 (6.0)	520 (6.3)	141 (5.0)	39 (5.4)
Anosmia (n, %)	424 (3.6)	334 (4.1)	79 (2.8)	11 (1.5)
Missing (n, %)	*855 (7.3)*	*593 (7.2)*	*216 (7.7)*	*46 (6.4)*
Runny nose (n, %)	416 (3.6)	301 (3.7)	91 (3.2)	24 (3.3)
Clinical signs at admission	9993 (85.3)	7005 (85.5)	2452 (87.3)	536 (74.7)
Abnormal pulmonary imaging (n, %)*	7396 (63.1)	5271 (64.4)	1835 (65.3)	290 (40.4)
Abnormal pulmonary auscultation (n, %)	5245 (44.8)	3701 (45.2)	1343 (47.8)	201 (28.0)
Dyspnea (n, %)	4966 (42.4)	3462 (42.3)	1196 (42.6)	308 (42.9)
Pharyngitis (n, %)	244 (2.1)	174 (2.1)	58 (2.1)	12 (1.7)
Coma (n, %)	72 (0.6)	50 (0.6)	16 (0.6)	6 (0.8)
Conjunctivitis (n, %)	57 (0.5)	37 (0.5)	18 (0.6)	2 (0.3)
Convulsions (n, %)	15 (0.1)	12 (0.1)	3 (0.1)	0 (0.0)

ACEI; Angiotensin converting enzyme inhibitors, ARBs. Angiotensin receptor blockers
** Reported as abnormal pulmonary imaging compatible with pneumonia*

Table 2 Supplemental. Results (OR, 95%CI) of variable selection models of conditions associated with ACEI/ARBs use among factors with COVID-19 prognosis[1]

Variable	Model 1	*p*-value	Model 2	*p*-value
Intercept	0.04 (0.03-0.05)	< 0.0001	0.03 (0.03-0.05)	< 0.001
Gender (male)	1.33 (1.21-1.47)	< 0.0001	1.26 (1.12-1.41)	< 0.001
Age	1.01 (1.01-1.02)	< 0.0001	1.01 (1.01-1.02)	< 0.001
CVD	1.71 (1.55-1.90)	< 0.0001	1.65 (1.46-1.87)	< 0.001
Diabetes	1.38 (1.24-1.54)	< 0.0001	1.37 (1.20-1.56)	< 0.001
HBP	5.65 (5.10-6.27)	< 0.0001	5.28 (4.66-6.00)	< 0.001
Obesity			1.33 (1.10-1.59)	< 0.01
Cognitive impairment			0.69 (0.58-0.82)	< 0.001

[1] *Backwards stepwise logistic regression with variable selection according to AIC; OR, odds ratio. Model 1 included: Gender, age, HBP, CVD, DM, chronic renal disease, chronic liver disease, chronic lung disease, solid malignant neoplasms, hematological cancers, immunodepression (N=10866); Model 2 included: Model 1 variables plus cognitive impairment, chronic neuro-muscular disease, and obesity, for which a high degree of missingness was observed and represents a complete case analysis (N=7,294)*

Table 3 Supplemental. State-arrival extended Cox-Markov models transitions hazard ratios (HR, 95%CI) as a function of ACEI/ARBs and identified confounders

Model 1

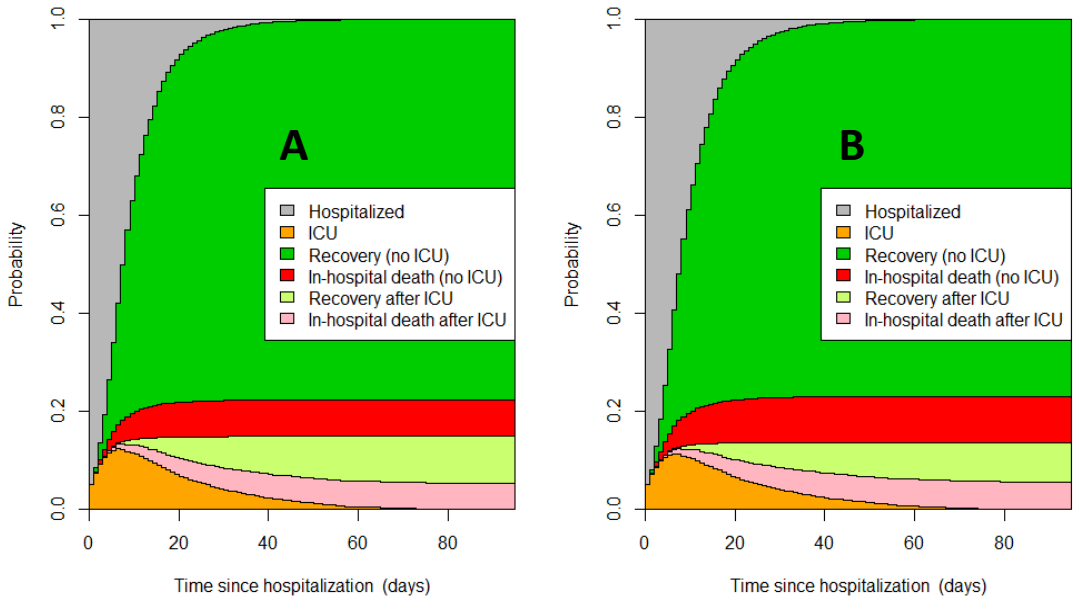
Transition		ACEI/ARBs use	Male gender	Age < 70	Age > 70	CVD	HBP	DM	Time to severity
1	Admission to Severity	1.15 (0.98, 1.36)	**1.83 (1.58, 2.12)**	**1.02 (1.01, 1.02)**	**0.90 (0.89, 0.91)**	0.96 (0.82, 1.12)	**1.35 (1.15, 1.58)**	0.94 (0.79, 1.11)	
		0.092	<0.0001	<0.0001	<0.0001	0.575	<0.0001	0.440	
2	Admission to Recovery	**1.07 (1.01, 1.13)**	**0.89 (0.85, 0.93)**	**0.97 (0.97, 0.97)**	**0.96 (0.96, 0.97)**	**0.86 (0.81, 0.91)**	**0.95 (0.89, 1.00)**	**0.92 (0.87, 0.98)**	
		0.027	<0.0001	<0.0001	<0.0001	<0.0001	0.043	0.007	
3	Admission to Death	**0.83 (0.75, 0.93)**	**1.45 (1.31, 1.59)**	**1.11 (1.09, 1.13)**	**1.05 (1.04, 1.05)**	**1.13 (1.02, 1.25)**	1.00 (0.90, 1.10)	1.09 (0.98, 1.22)	
		0.001	<0.0001	<0.0001	<0.0001	0.015	0.947	0.102	
4	Severity to recovery	1.16 (0.97, 1.38)	0.90 (0.77, 1.04)	**0.97 (0.96, 0.97)**	1.00 (0.98, 1.02)	1.03 (0.87, 1.21)	0.95 (0.81, 1.12)	1.01 (0.85, 1.19)	**0.95 (0.93, 0.97)**
		0.098	0.158	<0.0001	0.799	0.766	0.570	0.919	<0.0001
5	Severity to death	0.91 (0.73, 1.13)	1.11 (0.91, 1.36)	**1.05 (1.03, 1.06)**	1.05 (1.03, 1.07)	1.07 (0.88, 1.30)	0.90 (0.74, 1.11)	**1.25 (1.02, 1.53)**	1.02 (1.00, 1.04)
		0.381	0.316	<0.0001	<0.0001	0.494	0.326	0.034	0.056

Model 2

Transition		ACEI/ARBs use	Male gender	Age < 70	Age > 70	CVD	HBP	DM	Cognitive issues	Obesity	Time to severity
1	Admission to severity	1.10 (0.88, 1.36)	**1.71 (1.42, 2.08)**	**1.02 (1.01, 1.03)**	**0.92 (0.90, 0.93)**	0.91 (0.74, 1.12)	**1.45 (1.18, 1.79)**	0.96 (0.77, 1.19)	**0.52 (0.35, 0.77)**	**1.58 (1.24, 2.02)**	
		0.409	<0.0001	0.001	<0.0001	0.361	0.001	0.686	0.001	<0.0001	
2	Admission to recovery	1.05 (0.98, 1.13)	**0.89 (0.84, 0.94)**	**0.97 (0.97, 0.97)**	**0.97 (0.96, 0.97)**	**0.88 (0,82, 0.94)**	0.97 (0.91, 1.04)	0.93 (0.87, 1.00)	**0.83 (0.76, 0.91)**	1.01 (0.92, 1.11)	
		0.182	<0.0001	<0.0001	<0.0001	<0.0001	0.377	0.061	<0.0001	0.882	
3	Admission to death	**0.80 (0.70, 0.91)**	**1.48 (1.31, 1.66)**	**1.10 (1.07, 1.12)**	**1.05 (1.04, 1.05)**	**1.13 (1.00, 1.27)**	1.03 (0.91, 1.16)	1.11 (0.97, 1.27)	**1.36 (1.19, 1.55)**	0.97 (0.76, 1.24)	
		0.001	<0.0001	<0.0001	<0.0001	0.048	0.685	0.116	<0.0001	0.824	
4	Severity to recovery	1.16 (0.93, 1.45)	0.90 (0.75, 1.09)	**0.97 (0.96, 0.98)**	1.00 (0.97, 1.02)	1.12 (0.91, 1.38)	1.00 (0.81, 1.24)	0.95 (0.77, 1.16)	1.22 (0.84, 1.77)	0.97 (0.77, 1.22)	**0.94 (0.91, 0.97)**
		0.195	0.272	<0.0001	0.861	0.288	0.984	0.597	0.297	0.781	<0.0001
5	Severity to death	1.11 (0.83, 1.49)	1.22 (0.93, 1.60)	**1.04 (1.02, 1.06)**	**1.06 (1.03, 1.08)**	1.08 (0.82, 1.41)	0.81 (0.61, 1.08)	**1.44 (1.10, 1.90)**	0.89 (0.53, 1.50)	0.97 (0.69, 1.36)	**1.04 (1.01, 1.06)**
		0.485	0.146	<0.0001	<0.0001	0.591	0.150	0.008	0.668	0.860	0.003

ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers; CVD, cardiovascular disease; DM, diabetes mellitus; HBP, high blood pressure. Model 1: Adjusted for gender, age (years), CVD, HBP, DM, and time (days) to severity; Model 2: Further by prevalent obesity, and cognitive issues.

Figure 1 Supplemental.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8,9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	9,10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, and Fig 1
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-14, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	25, Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	26, Table 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*26, table 2*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	27, table 3
		(*b*) Report category boundaries when continuous variables were categorized	All tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	27, Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Insights into the association of ACEI/ARBs use and COVID-19 prognosis: A multi-state modelling study of nationwide hospital surveillance data from Belgium

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Insights into the association of ACEI/ARBs use and COVID-19 prognosis: A multi-state modelling study of nationwide hospital surveillance data from Belgium

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Keywords

Angiotensin-converting enzyme inhibitors (ACEI); Angiotensin-receptor blockers (ARBs); COVID-19; comorbidities; multi-state model.

Abstract

Objectives: The widespread use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) by chronic patients raised early concerns on the potential exacerbation of COVID-19 severity and fatality. Previous studies addressing this question have used standard methods that may lead to biased estimates when analyzing hospital data because of the presence of competing events and event-related dependency. We investigated the association of ACEI/ARBs use with COVID-19 disease outcomes using time-to-event data in a multi-state setting to account for competing events and minimize bias.

Setting: Nationwide surveillance data from 119 Belgian hospitals.

Participants: Medical records of 10,866 patients hospitalised from March 14 to June 14, 2020 with a confirmed SARS-CoV-19 infection and information about ACEI/ARBs use.

Primary outcome measure: Multi-state, multivariate Cox-Markov models were used to estimate the hazards of patients transitioning through health states from admission to discharge or death, along with transition probabilities calculated by combining the baseline cumulative hazard and regression coefficients.

Results: After accounting for potential confounders there was no discernable association between ACEI/ARBs use and transfer to intensive care (ICU). Contrastingly, for patients without ICU transfer, ACEI/ARBs use was associated with a modest increase in recovery (HR 1.07 [95%CI 1.01-1.13], p=0.027) and reduction in fatality (0.83, 0.75-0.93, p=0.001) transitions. For patients transferred to ICU admission, no evidence of an association between ACEI/ARBs use and recovery (1.16, 0.97-1.38, p=0.098) or in-hospital death (0.91, 0.73-1.12, p=0.381) was observed. Male gender and older age were significantly associated with higher risk of ICU admission or death. Chronic cardiometabolic comorbidities were also associated with less recovery.

Conclusions: For the first time, a multistate model was used to address magnitude and direction of the association of ACEI/ARBs use on COVID-19 progression. By minimizing bias, this study provided a robust indication of a protective, albeit modest, association with recovery and survival.

Keywords: Angiotensin-converting enzyme inhibitors (ACEI); Angiotensin-receptor blockers (ARBs); COVID-19; comorbidities; multi-state model.

Strengths and limitations of this study

- The study uses nationwide hospital surveillance data, and includes all general hospitals in Belgium.
- The use of a comprehensive database, but more so the utilization of models adequately fitting time-to-event data with mutually exclusive health states results in less probability of introducing biases and are crucial for correct evidence-based information for decision making.
- Only transfer to intensive care was linked to a calendar date and was therefore the only event which could be used as a proxy for severe disease state in our time-dependent model, indicating that our estimates might represent more a critical state of the patient.
- Information of ACEI/ARBs use was available at admission only, without any further information on the in-hospital use of ACEI/ARBs for those patients which could introduce a risk of immeasurable time bias if treatment discontinuation vs continuation has an impact on COVID-19 severity outcomes.

1. BACKGROUND

COVID-19 is known to affect more severily to older individuals, men and patients with chronic respiratory or cardiometabolic conditions such as cardiovascular disease (CVD), hypertension (HTN) and diabetes (DM) [1-3]. Also, common risk factors for chronic conditions, such as smoking and particularly obesity, have been identified as key predictors of hospitalization and critical illness, even in young adults with no underlying conditions [4 5]. While the pathogenesis of certain chronic diseases predisposes to severe COVID-19 outcomes, common chronic medications have been also a concern because of their potential interaction with the angiotensin-converting enzyme 2 (ACE2)[6]. SARS-CoV-2 binds to target cells using ACE2 in cell membranes[7], an enzyme that physiologically counters the renin-angiotensin-aldosterone system (RAAS) activation, degrading angiotensin II to attenuate its subsequent physiological action. Modulation of the RAAS is a common mode of action of the widely used antihypertensive drugs ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) which have been reported to upregulate ACE2 expression in the heart, and mostly in animal models [8-12]. This potential upregulation suggested that ACE2 expression may be increased in patients treated with ACEI or ARBs, potentially worsening further the prognosis of COVID-19 infection among chronic patients, and raising early concerns during the first phases of the outbreak of the SARS-CoV-2 pandemic [13 14]. As patients with chronic comorbidities were also identified as more vulnerable to severe COVID-19 disease, it is necessary to understand whether part of this vulnerability could be attributed to the use of ACEI/ARBs and to evaluate the risk of discontinuing this otherwise essential, first-line therapy, for hypertensive and diabetic patients.

To date, a number of studies addressing the potential effect of ACEI and ARBs on the prognosis of COVID-19 have been reported, mostly supporting the absence of harmful effects of these drugs on COVID-19 prognosis [15-32]. In these studies, a wide range of statistical methods have been used to test this hypothesis, including comparison of proportions, percentage points, logistic regression, or time-to-event analysis and Cox models. The use of standard methods for these particular analyses can

easily lead to biased estimates, in particular when analyzing hospital data because of the presence of competing events, such as death and recovery, and the time-dependency of these competing events [33 34]. As such, the analysis of the association of ACEI/ARBs on the progression of COVID-19 or related mortality requires the assessment of competing risks/events. Analyzing time-to-event data in a multi-state setting would better fit the true progression of COVID-19 in hospitalized patients, as shown by two studies using a multi-state-approach in the context of COVID-19 [35 36]. Multi-state models allow for studying clinically competing events (discharged alive vs deceased), as well as disease progression (e.g. in terms of hospital stay duration, transfer to intensive care units (ICU), treatment received), simultaneously over time. This multi-state model framework ensures avoiding bias that stems from censoring patients (informative censoring and/or selection bias) and time-dependent predictors (time-dependent bias), as well as circumvents event-related dependency by treating disease progression as a transient state that might influence the probability of experiencing a certain future outcome depending on patient's risk factors. While accounting for these biases, we revisited the the hypothesis of the potential association of ACEI/ARBs use in patient's prognosis during hospitalization using a competing risk multi-state model and nationwide hospital surveillance data on COVID-19 patients in Belgium.

2. PATIENTS AND METHODS

2.1. Data sources

All methods were carried out in accordance with relevant guidelines and regulations. Nationwide hospital surveillance data on COVID-19 patients in Belgium are routinely gathered by Sciensano, the Belgian Institute of Public Health, which is legally entitled institution for surveillance of infectious diseases in Belgium (Royal Decree of 21/03/2018). Retrieving informed consent was determined as a disproportional load on the hospital resources in the crisis situation. An information letter was given to the patients at the time of discharge which contained an explanation of their rights concerning the data that was gathered by Sciensano. The COVID-19 hospital surveillance was authorised by an

independent administrative authority protecting privacy and personal data and was approved by the ethical committee of Ghent University Hospital (BC-07507). Details on the Belgian COVID-19 hospital surveillance system have been previously published [37]. The system cover 119 hospitals in Belgium, who report standardized information on hospitalized COVID-19 patients collected through a structured questionnaire at hospital admission and discharge. An anonymized subset of data from Sciensano was shared with the Institute of Tropical Medicine through a secured data transfer platform applying data encryption. Ethical clearance was obtained from the Institutional Review Board (IRB) of the Institute of Tropical Medicine after revision of the research protocol num. 1393/20, 02/05/2020.

Variables collected at admission include the date of hospital admission, reason for hospitalization, symptoms, clinical signs, treatment with ACEI or ARBs, and demographic information such as age, gender, and the presence of chronic comorbidities. Information recorded at discharge includes laboratory values, details on COVID-19 specific treatments during hospital stay, date of discharge, health status at discharge, and measures on the severity of the disease such as the need for transfer to ICU, invasive ventilation support and/or oxygenation by extracorporeal membrane oxygenation (ECMO), and the development of a bacterial and/or fungal superinfection, pneumonia, and/or acute respiratory distress syndrome (ARDS). Dates for these severe events were only available for ICU transfer.

2.2. Study population

Adult COVID-19 patients with a SARS-CoV-19 infection confirmed by polymerase chain reaction (PCR), and/or suggestive imaging alterations on chest CT combined with typical clinical presentation, at admission or while hospitalized in Belgium from March 14 to June 14, 2020 were considered as COVID-19 patients (n=16,341). Of these, patients with completed questionnaires both on admission and discharge (12,109 patients, 74.1%) were selected. Information on patients admitted to hospitals before March 1 2020 (270, 1.65%) for reasons other than COVID-19, and infected while hospitalized

was also removed. Furthermore, information on patients with implausible admission dates was removed, including: Date of discharge before date of admission (42 patients, 0.25%); Date of ICU transfer preceding date of admission (31 patients, 0.19%); Date of discharge before date of ICU transfer (2 patients, 0.01%); Date of discharge preceding the date of ICU discharge if the difference was more than 1 day (47 patients, 0.28%). The final dataset for descpritive analyses included information on 11717 COVID-19 patients. For the multivariate multi-state model, patients with unknown use of ACE/ARBs (718 patients, 6.12%) were also excluded, along with those missing information on gender (118 patients, 0.72%) or unknown transfer to ICU (15, 0.09%). The final dataset for the multi-state model contained information from 103 hospitals in Belgium and 10,866 COVID-19 patients, including 539 patients (5%) that were admitted directly to ICU.

2.3. Study outcomes

Patients were considered to have recovered when their status at hospital discharge was recorded as “cured” or “other”. In the latter case, it was assumed they were allowed to recover at home, revalidation center or nursing home. Patients were considered as an in-hospital death when their status at discharge was recorded as “death”. Patients were considered lost to follow up when their status at discharge was recorded as “unknown” or when they were transferred to another hospital (recorded as status at discharge = “transfer to another hospital”), as no further information was available. Severe COVID-19 was captured in the database as an illness that required ECMO or artificial ventilation, or to have experienced ARDS, pneumonia, bacterial and/or fungal co-infection, or required transfer to or treament at ICU. Among these, event date was only available for transfer to ICU, and only this variable could be therefore selected for the models as time-defined severity outcome. Incorporating the intermediate event of ICU transfer allows for a patient’s risk profile for recovery and death to be different before and after this intermediate event. In order to do so, time to severe illness was defined as the time passed from the date of hospital admission to the date of

transfer to ICU, while length of hospital stay was defined as the date from hospital admission to the date of hospital discharge (either recovery, in-hospital death, or lost to follow-up).

2.4. Information on ACEI/ARBs and conditions related to COVID-19 prognosis

A dedicated section in the admission dataset covered the use of ACEI, ARBs or both, without specification of the specific drug. The admission database contained information on the following factors associated with COVID-19[38]. Demographics (age and gender), risk factors (current smoking, high blood pressure (HBP), and obesity), prevalent comorbidities (DM, chronic renal disease, CVD, chronic lung disease, chronic liver disease, malignant solid neoplasms, hematological cancers, and immunosuppression). Smoking status was only available for 53% of the patients. Obesity also presented a large number of missing values (33.2%) because this variable was only recorded after April 3, 2020. Similarly, there were also missing values for cognitive issues (5.7%) as this variable was only recorded after March 23, 2020.

3. STATISTICAL MODEL

Patient's characteristics at hospital admission, ICU stay, and at hospital discharge were visualized on histograms and summarized as means and standard deviations or counts and percentages for continuous and categorical variables, respectively. Descriptive analyses were provided for patients overall and stratified by ACEI/ARBs use, including unknown use.

To study the association of ACEI/ARBs on COVID-19 progression on a multivariate multi-state model, a first model for identiying confounders was carried out. A backwards stepwise logistic regression with ACEI/ARBs use as dependent variable, and including factors and conditions previously associated with COVID-19 outcomes and present in the database [39 40], was used to inform the selection of potential confounders based on Akaike's information criterion (AIC). The variables used in the variable selection model were: gender, age, HBP, CVD, DM, obesity, chronic renal disease, chronic liver disease, chronic lung disease, solid malignant neoplasms, hematological cancers,

immunodepression, and cognitive impairment. Two models were used depending on the availability of data, a first model (model 1) excluding variables collected at a later date (obesity, and cognitive issues) and using a full dataset (N=10,866), and a complete case analysis (model 2) excluding patients with missing data for obesity and cognitive issues (N=7,303).

We devised a multi-state model reflecting the progression of patients from hospital admission to discharge accounting for the patient's characteristics identified to be potential confounders, and introducing ACEI/ABRs use as dependent variable. The model starts with one initial state (hospitalization), a potential (transient) state defined as ICU transfer (as a proxy for severe COVID-19 disease, as only ICU transfer had an associated date in the database) and two absorbing states (in-hospital death, and recovery). The multi-state model is characterized by transition hazards between the states; defined as the instantaneous risk for moving from one health state to another. The transitions hazards are used to calculate transition probabilities, as the conditional probabilities of experiencing future outcomes, given the history and a particular set of prognostic factors (model covariates) for a given patient. The four-state model thereby comprised five possible patient's transitions; 1) hospitalization to ICU, 2) hospitalization to recovery, 3) hospitalization to in-hospital death, 4) ICU to recovery, and 5) ICU to in-hospital death, as presented in Figure 1. A Cox-Markov model for the regression on the transition specific hazards was fitted using the *coxph* and *msfit* functions in R *survival* package[41]. This approach is equivalent of constructing five separate Cox regression models, one for each transition hazard. The cumulative baseline transition hazard (all covariate values equal to the reference value) was estimated by the Breslow estimator with the Aalen estimator of variance [42]. We integrated these separate Cox models in a multi-state framework studying different outcomes simultaneously and allowing the calculation of transition probabilities. The transition probabilities were then estimated by combining the baseline cumulative hazard and regression coefficients. Using R, the *mstate* package and *msfit* function was applied to obtain cumulative (baseline) transition hazards and the function *probtrans* to obtain the transition probabilities[43]. Estimates obtained from the Cox-Markov models are displayed in a table and

significance is established at the 5% significance level. Cumulative (baseline) transition hazard plots and transition probability plots were also generated for visual aid. In a setting with covariates, a regression model for the transition specific hazards was used, whereby the covariates may help to explain the difference in transition hazards. Model diagnostics were performed to check model assumptions of proportional hazards, linearity, and interactions. Assumptions to the Markov model were assessed by including time from hospital admission to ICU transfer in the model for transition 4 and transition 5. A relaxation of the Markov assumption was also explored in the analysis.

4. Patient and public involvement

As a secondary data analysis of COVID-19 surveillance data this study did not involve patients or the public in the design, conduct or dissemination plans.

5. RESULTS

5.1. Descriptive analysis

From the 11,717 patients available for this analysis, almost of all them (94.2%) presented symptoms or clinical signs compatible with COVID-19 at admission (Supplemental Table 1). Most frequent symptoms were fever (61.3%) and cough (53.2%), and most frequent signs were abnormal pulmonary imaging (63.1%) compatible with viral pneumonia, abnormal auscultation (44.8%), and dyspnea (42.4%). On admission, 15.1% of patients had a record of taking ACEI, and 8.5% ARBs, with only 0.4% taking both ACEI and ARBs. For the purpose of this analysis these patients were merged as ACEI/ARBs users. The majority of patients (69.9%) were non-users of ACEI/ARBs versus 23.9% of users, and only for a small proportion (6.1%) of patients the use of ACEI/ARBs was unknown (Table 1). No difference was seen in the frequency of signs and symptoms reported according to ACEI/ARBs use (Supplemental Table 1). Patients using ACEI/ARBs were markedly older (median [IQR] age 76 [65-84] years) than non-users (67 [53-81]) while no gender-differences were observed. As expected, ACEI/ARBs users presented more frequently (74.4%) HBP than non-users (39.2%), as well as chronic

lung disease (16.8% vs 14.4%), chronic renal disease (19.3% vs 11.1%), DM (33.3% vs 18.1%), and particularly CVD (53.1% vs 28.4%). Multiple comorbidities (HBP, DM and CVD) were more frequent among ACEI/ABRs users (15.1%) than non users (4.9%) (Table 1). During hospital stay, over 80% of COVID-19 patients experienced one severe episode of either pneumonia, superinfection, ARDS, or mechanical ventilation, and 25.9% of patients had two or more severe episodes (Table 2). The most common manifestation of COVID-19 severity was pneumonia (79.1%), followed by other infections (19.4%), ARDS (12.7%), and artificial ventilation (7.6%). Frequency of severe conditions was nearly the same for both ACEI/ARBs users and non-users (27.8% versus 25.4%). Of all admitted patients, 1,518 (13.0%) were transferred to ICU, mostly those with severe pneumonia (93.7%), or in need of artificial ventilation (58.0%), and remained at ICU for a mean duration of 11.5 ± 10.7 days. Transfer to ICU was marginally more frequent among ACEI/ARBs users (15.1% versus 12.1%). Almost 78% of the patients admitted to Belgian hospitals recovered from COVID-19, either during hospitalization (51.2%) or at home or revalidation centre or nursing home (26.4%) after an average 12.6 ± 10.9 days in the hospital. Only 2% of patient's information was lost to follow-up (transferred to another health care provider or unknown status at discharge).

5.2. Multi-state model

A multivariate state-arrival extended Cox-Markov model was used to study the potentially different progression of COVID-19 patients through health states during hospitalization according to the use of ACEI/ARBs. Possible transitions, and number of patients in each health state are represented in Figure 1. The selection of variables for adjusting the models were based on backwards stepwise logistic regression of ACEI/ARBs use as a function of potential confounding factors associated with COVID-19 recorded at admission (Table 2 Supplemental). A first model (model 1) using all available patients, identified five variables associated with the use of ACEI/ARBs and COVID-19: male gender (OR 1.33, 95%CI 1.21-1.47), older age (1.01, 1.01- 1.02 per 1-year increase), and prevalent CVD (1.71, 1.55 -1.90), diabetes (1.38, 1.24-1.54), and HBP (5.65, 5.10-6.27). Additionally, a

second model (model 2) was used in sensitivity analysis including additional covariates (prevalent obesity and cognitive impairment) that were only available in a subset (62%) of patients (Table 2 Supplemental). Because very few patients were asymptomatic on admission it was deemed unnecessary to adjust the regression models for severity of disease at admission. For 16 patients (0.1%) it was unknown whether they were transferred to ICU. These patients are therefore excluded from the multistate Cox-Markov regression analysis.

Plots for the cumulative hazard and transition probability between health states considering ACEI/ARBs use were obtained by setting all model covariates to reference values (female gender, no CVD, no HBP, and no DM), and median (70 years) age Figure 2. When looking at the cumulative hazard for the five possible transitions (Figure 2A), the hazard for recovery was markedly greater than that of in-hospital death. In comparison with the other cumulative hazards, the hazard for transfer to ICU was substantially smaller, representative of most COVID-19 patients not needing intensive care, or not meeting criteria for admission (for instance after evaluation of frailty, and chance of survival). Transfer to ICU was associated with increased hazard for in-hospital death and reduced hazard for recovery. The use of ACEI/ARBs was associated with a modest but significant association with the hazard of transition 2 (more recovery) and 3 (less in-hospital death), from admission. The use of ACEI/ARBs was not observed to be associated with transfer to ICU (transition 1), nor with recovery (transition 4) or in-hospital death (transition 5) after ICU. Overall, the probability of being transferred to ICU was, for most patients, less than that of recovery (Figure 2B). However, those needing ICU had a reduced probability of recovery and greater probability to decease in the hospital than those patients not transferred to ICU (Figure 2C).

The estimates for the transition hazards for ACEI/ARBs use accounting for identified confounding in the potential association woth COVID-19 severity/fatality are presented in Table 3. In multivariate models, the use of ACE/ARBs was associated (HR 1.07, 95%CI 1.01-1.13) with more recovery, and less death (0.83, 0.75-0.93). Even though there was a significant association between ACEI/ARBs use the hazard of more recovery (transition 2), and less in-hospital death (transition 3)

this effect is modest, especially when reviewing state-occupation probabilities (Figure 1 Supplemental). In respect to the adjusting variables (Table 3 Supplemental), male gender and HBP were associated with transfer to ICU (severity), and older age also influenced this transition. Similarly, male gender, and older age, as well as prevalent CVD, HBP or DM were associated with less recovery. Similar to transfer to ICU, progression to death was associated with male gender and age, as well as with prevalent CVD. No other comorbidity included in this model (i.e. associated with ACEI/ARBs use) appeared to be associated with fatality. For severe patients (transferred to ICU) recovery or death depended mostly on age, albeit fatal COVID-19 was also associated with the presence of DM, and a lengthier period between admission and ICU was significantly associated with less recovery after ICU (Table 3 Supplemental). The impact of further adjustment for variables identified during confounder selection (obesity and cognitive issues) in the state transition of COVID-19 patients during hospitalization, resulted in loss of more than half of all patients due to missing values (Table 1). While estimated hazards for previous factors remained similar, the presence of cognitive issues was statistically significantly associated with transitions 1, 2, and 3 (i.e. less transfer to ICU, less recovery, and more in-hospital death), and obesity was strongly and statistically significantly associated with transition 1 only (more transfer to ICU). In this complete-case model, after additional adjustment for obesity and cognitive issues, the HR for ACEI/ABRs use for transition 2 (admission to recovery) did not remain significant probably due to a decreased statistical power, since the point estimates were similar.

6. DISCUSSION

In this study, a competing risk multistate model has been developed for the first time to address the magnitude and direction of the association of ACEI/ARBs use in COVID-19 prognosis. Our analyses indicate a protective association of ACEI/ARBs use, with increase recovery and survival, once important confounding factors such as age, particularly 70 and over, and male gender are accounted for. Chronic comorbidities such as CVD, HBP, and DM are also associated with less recovery in this

model setting. Although there is a protective association of ACEI/ARBs use on COVID-19 in-hospital death and more recovery, this association is modest, especially when looking at the state-occupation probabilities. In our model, once the patient progresses to a severe state, no association of ACEI/ARBs use was observed in the transition probabilities to recovery or in-hospital death; only older age and prevalent DM, remained significant covariates in our model, arguably because of the smaller sample size (transfer to ICU occurred only for 13% of patients). Previous studies using the same data source identified other comorbidities as independent risk factors for COVID-19 severity/death in ICU patients, including chronic pulmonary disease, chronic renald disease, and immunosuppression [44]. Although we accounted for these factors in our model selection, they were not selected as they are not considered to be related to the use of ACEI/ARBs but may nonetheless constitute an independent risk factors for severity.

Because of the important clinical relevance, there have been numerous reports on studies of the potential association between ACEI/ARBs and (worse) prognosis of COVID-19. Early studies of smaller sample size and mostly descriptive design pointed to either no association or moderately lower rates of severe disease among ACEI/ARBs users [15-20]. Further retrospective analysis involving larger patient samples generally reported a lack of association [21]. A population-based study in Italy's Lombardy region involving 6,272 cases identified across the Regional Health Service and matched 1:5 to population-based control, found no association between the use of ACEI (adjusted OR 0.91, 95%CI 0.69-1.21) or ARBs (adjusted OR 0.83, 95%CI 0.63-1.10) and severe/fatal COVID-19 [22]. Similarly, a case-control study in the Spanish region of Madrid with data on 1,139 hospitalized cases matched 1:10 to population controls found no association (adjusted OR 0.94, 95%CI 0.77-1.15) of ACEI/ARBs use and severe or fatal disease [23]. Analyzing data from patients in the New York University Langone Health electronic health record who had COVID-19 test results (12,594 patients), neither an increased likelihood of a positive test nor a severe disease status was observed for patients using ACEI/ARBs (or any other RAAS medication) using propensity score matching [24]. In a nationwide study in Korea using insurance claims of 66,793 individuals tested for COVID-19, the use of ACEI/ARBs was

not associated with a higher risk of mortality (adjusted OR 0.88, 95%CI 0.53-1.44) [25]. Similarly, a large retrospective analysis of an Italian registry cohort including 43,000 patients concluded that neither ACEI (adjusted HR 0.97, 95%CI 0.89-1.06) or ARB (adjusted HR 0.98, 95% CI 0.89-1.06) use was associated with either an increased or decreased risk of all-cause mortality [26]. A multicenter study with 1,128 hypertensive patients, and using mixed-effect Cox models (site as a random effect, and model adjusted for age, gender, comorbidities, and in-hospital medications) reported a lower risk for all-cause mortality in the ACEI/ARB patients versus the non-ACEI/ARB group (adjusted HR 0.42, 95%CI 0.19-0.92), and further compared with the use of other antihypertensive drugs, (adjusted HR 0.30, 95%CI, 0.12-0.70) [27]. Previous studies using Cox models reported also a reduced mortality risk for patients using ACEI/ARBs [27 28]. In others, albeit not statistically significant, estimates were very similar to the ones reported in our study for mortality (adjusted HR 0.83, 95%CI 0.67-1.03) and for severe disease (adjusted HR 1.15, 95%CI 0.95-1.41) [29]. Similarly, but outside of the hospital setting, studies with data from general practitioners in England, found a strong association of ACEI/ARBs use and a reduced risk of COVID-19 disease (HR 0.63, 95%CI 0.59-0.67) albeit not severity (HR 1.02, 95%CI 0.83-1.25), and marked interactions with ethnicity with higher risks observed for Black Africans compared to Whites[30]. Variations observed between different ethnicities raise the possibility of specific associations of ACEI/ARBs on COVID-19 disease susceptibility and severity which deserves further study. Furthermore, three review papers on the topic have concluded there is either no difference or a reduced risk when looking at mortality and/or severe disease [21 31 32], and no evidence to support discontinuing the treatment with ACEI/ARBs [45]. This substantial body of evidence seems aligned with recent findings from clinical studies that do not support the hyphothesis of an increased expression of ACE2 in chronic patients treated with ACEI or ARBs as a driver of severe COVID-19 [10-12].

Whereas the results on an increased risk of severe/fatal COVID-19 in association with the outpatient use of ACEIs/ARBs appear to point in the same direction, studies on the potential role of in-hospital use of ACEI/ARBs have described a protective association of continuing the treatment throughout hospitalization [27 46 47]. In a multi-center study including 1,128 adult patients with HTN and

diagnosed with COVID-19, including 188 taking ACEI/ARB and 940 without using ACEI/ARB during hospitalization, the risk for all-cause mortality was lower in the ACEI/ARB group versus the non-ACEI/ARB group (HR 0.42, 95% CI, 0.19–0.92) [27]. Similarly, a study conducted in 347 patients hospitalized for COVID-19 in Paris (France) analysing the association between in-hospital exposure of ACEI/ARBs and mortality within 30 days of hospital admission using logistic regression analysis, no association (OR 0.62, 95%CI: 0.25-1.48) based on chronic exposure but a protective association (OR 0.25, 95%CI: 0.09-0.65) based on in-hospital exposure was observed.[46] Among 397 patients with COVID-19 addmited to hospitals in Rozzano-Milan (Italy) the risk of mortality was significantly reduced in patients who continued ACEI/ARBs as compared with those who discontinued and those not taking ACEI/ARB therapy (OR 0.14, [95%CI: 0.03-0.66]) [47]. Using data from 7 hospitals in Madrid (Spain), no difference in mortality rates was observed among patients that discontinued (340 patients) ACEI/ARBs treatment (HR 1.01, [95%CI 0.70–1.46]) versus those that continued (280 patients) [48]. Furthermore, recent data from two randomized trials could not confirm any impact on clinical outcomes in hospitalized COVID-19 patients discontinuing treatment of ACEI or ARBs as compared with those continuing their treatment [49 50], hereby further supporting a safe ACEI/ARBS treatment continuation if there is an indication for treatment.

Our study builds on these previous reports where standard statistical models were used for analysis, introducing a model framework overcoming the risk of biases [33]. Logistic-based regression models might introduce selection bias by excluding patients who are still hospitalized at the last follow-up, hence the need for time-to-event models that allow patient censoring [33]. These time-to-event models, such as Cox regression models, should preferably account for the presence of competing risks to avoid informative censoring bias, and for time-dependent predictors to appropriately handle index time or follow-up time of covariates[33 49]. Integrating standard Cox models into a multi-state framework allows the study of separate outcomes simultaneously and allows the calculation of the transition probabilities, adding a layer of interpretation. In this way, by

incorporating event-related dependency, i.e., transitions to intermediate events that likely influence disease progression, the multi-state model more accurately describes the evolution of COVID-19 in hospitalized patients [51]. In the present stud, we used a time-to-event analysis in a multi-state framework considering competing risks to account appropriately for censoring [52], thereby robustly showing a modest, yet significant, positive association of ACEI/ARBs use in recovery and survival of hospitalized COVID-19 patients accounting for confounding factors.

Our study uses nationwide hospital surveillance data, with mandatory participation, and includes all general hospitals (including university hospitals) in Belgium, both those managed by a public authority and privately managed are represented. The surveillance does not cover psychiatric hospitals or specialist hospitals [37]. The use of comprehensive datasets, but more so the utilization of models adequately fitting to time-to-event hospital data with mutually exclusive health states results in less probability of introducing biases and are crucial for correct evidence-based information for decision making. Our study makes some assumptions, and unknowns such as the lack of information on ACEI/ARBs exact indication and whether their use was continued after admission. This lack of accounting for time-varying exposure introduces a risk of immeasurable time bias[34], as seen in many reports, though assumed to be minimal because no difference in COVID-19 severity outcomes between treatment discontinuation vs continuation [49 50]. Our models are not adjusted for severity at baseline since we reasoned that hospital admission was already an indicator of severe disease and 94% of patients had symptoms compatible with COVID-19 diagnosis at baseline. Further, even though other events potentially indicating severity (ECMO, ARDS, pneumonia, bacterial and/or fungal co-infection) were available in the database, only transfer to ICU was linked to a calendar date and was therefore the only event which could be used as a proxy for severe health state in our time-dependent model, indicating that our estimates might represent more a critical state of the patient. In addition, admission to intensive care is not solely based on the clinical status of the patient, but also on other criteria such as frailty. Also, ICU admission criteria might have been more restrictive in

the peak period of the epidemic whilst certain ICU were overloaded. Because the surveillance data is limited to the most important variables, we cannot discard the possibility of some degree of residual confounding in our results. An important limitation of our main analysis is the impossibility of adjusting our models for smoking status, obesity and cognitive issues at baseline. Using available smoking information was not deemed appropriate due to the excessive number of missing values, and the lack of information of the reason for the incomplete data. We used, however, data on obesity and cognitive issues, which collection was introduced later, in a complete case analysis to confirm the results obtained in the main model. Nevertheless, these analyses on a reduced sample of patients should be interpreted with caution as a time effect is likely present because of the late data collection. Finally, our analyses are based on patient's medical files and rely on how clinicians reported clinical observations and anamnesis which might vary across hospitals, and are representative of the first so called wave of the epidemic in Belgium, and associations might differ in subsequent studies and in other settings.

7. CONCLUSIONS

After adjustment for important confounders there is modest, yet significant, positive association of ACEI/ARBs use on recovery and survival of hospitalized COVID-19 patients, without affecting admission to intensive care. This supports the use of ACEI/ARB in those patients who need them, also when needing hospitalization from COVID-19. These findings are based on an analytical model that adequately fits hospital data, where patients progress across different, competing, health states providing a more complete and acurate view of the research question within a reduced risk of bias framework. Integrating standard cox models into a multi-state framework allows the study of separate outcomes simultaneously and allows the calculation of the transition probabilities, adding a layer of interpretation. Multi-state models should be favoured over separate survival analysis when

competing risks are present, and traditional methods such as logit functions should be discouraged when time-to-event is available.

Contributorship statement

JLP, MvdS, MAW, DV conceptualized the study. DV performed data curation and provided data. JLP, EG, EM, DS developed methodology, and performed analysis. JLP supervised the study, and drafted the manuscript. All authors have critically reviewed, commented, and approved the manuscript before submission.

Competing interest

The authors declare that they have no competing interests.

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Data sharing statement

The data that support the findings of this study are available from Sciensano but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Sciensano.

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FIGURE TITLES

Figure 1. Schematic representation of the competing risk multi-state model and transition event matrix (number (%) patients in each transition.

*Figure footnote: Numbers in superscript represent transitions depicted in the figure.*539 patients were directly admitted to ICU*

Figure 2. Plots for cumulative transition hazards (A), and state transition probabilities (B), and transition probabilities after transfer to intensive care (C) in a multi-state competing risk model considering ACEI/ARBs use (dashed line) versus no use (solid line).

Figure 1 Supplemental. Staked probability plot of the state-occupation probabilities in a multi-state competing risk model considering ACEI/ARBs use (A) versus no use (B).

Table 1. COVID-19 patient's characteristics at hospital admission according to ACEI/ARBs use

	Total	ACEI/ARBs		
	(n = 11717)	No use (n = 8189, 69.9%)	Use (n = 2810, 23.9%)	Unknown use (n = 718, 6.1%)
Demographics				
Age (years) (mean (SD))	67.82 (17.17)	65.70 (17.90)	74.08 (12.85)	67.47 (17.50)
Equal or more than 70 years old (n, %)	6044 (51.6)	3791 (46.3)	1886 (67.1)	367 (51.1)
Sex (n, % males)	6154 (52.5)	4227 (51.6)	1562 (55.6)	365 (50.8)
Missing (n, %)	*129 (1.1)*	*93 (1.1)*	*25 (0.9)*	*11 (1.5)*
Risk factors				
Smokers (n, %)	606 (5.2)	440 (5.4)	142 (5.1)	24 (3.3)
Missing (n, %)	*5413 (46.2)*	*3667 (44.8))*	*1160 (41.3)*	*586 (81.6)*
Flu vaccination (n, %)	841 (7.2)	572 (7.0)	250 (8.9)	19 (2.6)
Missing (n, %)	*10076 (86.0)*	*7018 (85.7)*	*2374 (84.5)*	*684 (95.3)*
Obesity (n, %)*	782 (6.7)	478 (5.8)	271 (9.6)	33 (4.6)
Missing (n, %)	*3887 (33.2)*	*2735 (33.4)*	*870 (31.0)*	*282 (39.3)*
Chronic comorbidities				
HBP (n, %)	4593 (39.2)	2343 (28.6)	2090 (74.4)	160 (22.3)
DM (n, %)	2522 (21.5)	1486 (18.1)	936 (33.3)	100 (13.9)
Chronic renal disease (n, %)	1513 (12.9)	911 (11.1)	541 (19.3)	61 (8.5)
CVD (n, %)	3984 (34.0)	2326 (28.4)	1493 (53.1)	165 (23.0)
Chronic lung disease (n, %)	1731 (14.8)	1180 (14.4)	473 (16.8)	78 (10.9)
Cognitive impairment (n, %)**	1320 (11.3)	922 (11.3)	331 (11.8)	67 (9.3)
Missing (n, %)	*668 (5.7)*	*461 (5.6)*	*173 (6.2)*	*34 (4.7)*
Chronic neuro-muscular disease (n, %)	993 (8.5)	704 (8.6)	241 (8.6)	48 (6.7)
Solid malignant neoplasms (n, %)	990 (8.4)	697 (8.5)	261 (9.3)	32 (4.5)
Chronic liver disease (n, %)	301 (2.6)	210 (2.6)	79 (2.8)	12 (1.7)
Immunodepression (n, %)	297 (2.5)	224 (2.7)	64 (2.3)	9 (1.3)
Hematological cancers (n, %)	216 (1.8)	154 (1.9)	56 (2.0)	6 (0.8)
Combination of comorbidities				
None (n, %)	4760 (40.6)	4145 (50.6)	192 (6.8)	423 (58.9)
CVD & HBP (n, %)	1386 (11.8)	713 (8.7)	633 (22.5)	41 (5.7)
CVD & DM (n, %)	385 (3.3)	248 (3.0)	113 (4.0)	24 (3.3)
HBP & DM (n, %)	682 (5.8)	348 (4.2)	309 (11.0)	25 (3.5)
CVD & HBP & DM (n, %)	401 (50.6)	401 (4.9)	423 (15.1)	20 (2.8)

*ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers; CVD, cardiovascular disease; DM, diabetes mellitus; HBP, high blood pressure. *Values only collected after April 3, 2020. **Values only reported after March 23, 2020.*

Table 2. Frequency of severity events among COVID-19 patients during hospital stay and recorded outcomes at discharge according to ACEI/ARBs use at admission

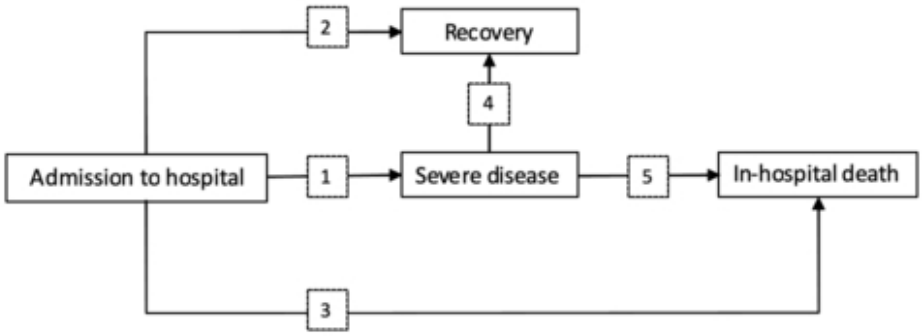
		ACEI/ARBs		
	Total (n = 11717)	**No use (n = 8189, 69.9%)**	**Use (n = 2810, 23.9%)**	**Unknown use (n = 718, 6.1%)**
Severe conditions				
Pneumonia (n, %)	9265 (79.1)	6501 (79.4)	2260 (80.4)	504 (70.2)
Missing (n, %)	*532 (4.5)*	*372 (4.5)*	*73 (73)*	*87 (87)*
Superinfection (n, %)	2268 (19.4)	1548 (18.9)	589 (21.0)	131 (18.2)
Missing (n, %)	*1277 (10.9)*	*820 (10.0)*	*320 (11.4)*	*137 (19.1)*
ARDS (n, %)	1492 (12.7)	996 (12.2)	389 (13.8)	107 (14.9)
Missing (n, %)	*1047 (8.9)*	*671 (8.2)*	*263 (9.4)*	*113 (15.7)*
Mechanical ventilation (n, %)	893 (7.6)	571 (7.0)	249 (8.9)	73 (10.2)
Missing (n, %)	*627 (5.4)*	*383 (4.7)*	*170 (6.0)*	*74 (10.3)*
Number of severe conditions (n, %)				
None	2143 (18.3)	1492 (18.2)	465 (16.5)	186 (25.9)
One	6537 (55.8)	4620 (56.4)	1565 (55.7)	352 (49.0)
Two or more	3037 (25.9)	2077 (25.4)	780 (27.8)	180 (25.1)
Intensive care				
Transfer to ICU (n, %)	1518 (13.0)	990 (12.1)	425 (15.1)	103 (14.3)
Missing (n, %)	*16 (0.1)*	*16 (0.2)*	*0 (0)*	*0 (0)*
Transfer to ICU + pneumonia (n, %)	1423 (93.7)	932 (94.1)	395 (92.9)	96 (93.2)
Transfer to ICU + superinfection (n, %)	653 (43.0)	423 (42.7)	181 (42.6)	49 (47.6)
Transfer to ICU + ARDs (n, %)	831 (54.7)	547 (55.3)	224 (52.7)	60 (58.3)
Transfer to ICU + mechanical ventilation (n, %)	880 (58.0)	561 (56.7)	246 (57.9)	73 (70.9)
Length (days) of ICU stay (mean (SD))	11.5 (10.7)	11.415 (10.7)	11.3 (10.8)	12.9 (11.0)
Discharge status				
Recovered at discharge (n, %)	6003 (51.2)	4244 (51.8)	1378 (49.0)	381 (53.1)
Recovered at home (n, %)	3093 (26.4)	2201 (26.9)	722 (25.7)	170 (23.7)
In-hospital death (n, %)	2388 (20.4)	1574 (19.2)	622 (23.6)	152 (21.2)
Transferred (n, %)	201 (1.7)	149 (51.8)	44 (49.0)	8 (53.1)
Unknown (n, %)	32 (0.3)	21 (0.3)	4 (0.1)	7 (1.0)
Length (days) of hospital stay (mean (SD))	12.6 (10.9)	12.1 (10.5)	13.9 (11. 7)	12.2 (11.6

ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Table 3. State-arrival extended Cox-Markov multivariate model's transitions hazard ratios (HR, 95%CI) as a function of ACEI/ARBs

Transition		ACEI/ABRs use			
		Model 1	*p*-value	Model 2	*p*-value
1	**Admission → Severity**	1.15 (0.98, 1.36)	0.092	1.10 (0.88, 1.36)	0.409
2	**Admission → Recovery**	**1.07 (1.01, 1.13)**	0.027	1.05 (0.98, 1.13)	0.182
3	**Admission → Death**	**0.83 (0.75, 0.93)**	0.001	**0.80 (0.70, 0.91)**	0.001
4	**Severity → Recovery**	1.16 (0.97, 1.38)	0.098	1.16 (0.93, 1.45)	0.195
5	**Severity → Death**	0.91 (0.73, 1.13)	0.381	1.11 (0.83, 1.49)	0.485

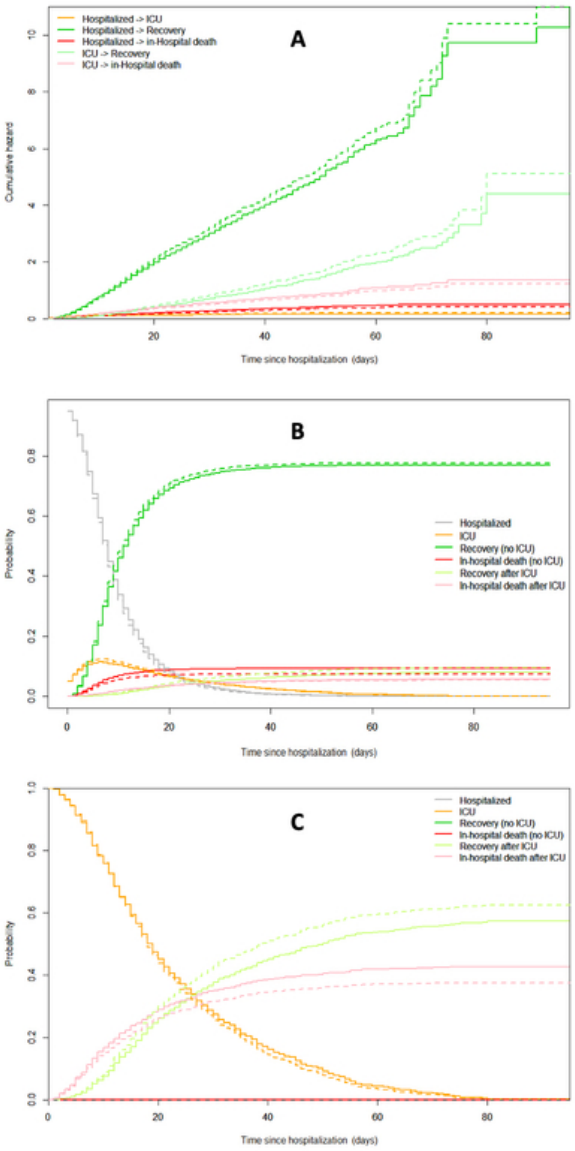
ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers Model 1: Adjusted for gender, age (years), prevalent CVD, HBP, DM, and time (days) to severity; Model 2: Further by prevalent obesity, and cognitive issues.



From	To Admission	Severity	Recovery	Death	No event	Total
Admission	0	863 (8.4)[1]	7633 (73.9)[2]	1738 (16.8)[3]	93 (0.9)	10327
Severity	0	0	817 (58.3)[4]	468 (33.4)[5]	117 (8.3)	1402*
Recovery	0	0	0	0	8450 (100)	8450
Death	0	0	0	0	2206 (100)	2206

Schematic representation of the competing risk multi-state model and transition event matrix (number (%) patients in each transition

21x12mm (600 x 600 DPI)



Plots for cumulative transition hazards (A), and state transition probabilities (B), and transition probabilities after transfer to intensive care (C) in a multi-state competing risk model considering ACEI/ARBs use (dashed line) versus no use (solid line).

17x33mm (600 x 600 DPI)

SUPPLEMENTAL MATERIAL

Table 1 Supplemental. Frequency of symptoms and clinical signs compatible with COVID-19 at hospital admission according to ACEI/ARBs use

	Total	ACEI/ARBs		
	(n = 11717)	No use (n = 8189, 69.9%)	Use (n = 2810, 23.9%)	Unknown use (n = 718, 6.1%)
Symptoms at admission	11039 (94.2)	7705 (94.1)	2673 (95.1)	661 (92.1)
Fever (n, %)	7187 (61.3)	5112 (62.4)	1653 (58.8)	422 (58.8)
Cough (n, %)	6231 (53.2)	4444 (54.3)	1438 (51.2)	349 (48.6)
Breathlessness (n, %)	5997 (51.2)	4194 (51.2)	1349 (52.0)	376 (47.6)
Weakness (n, %)	4672 (39.9)	3253 (39.7)	1153 (41.0)	266 (37.0)
Pain (n, %)	2622 (22.4)	1931 (23.6)	544 (19.4)	147 (20.5)
Diarrhea (n, %)	1673 (14.3)	1173 (14.3)	438 (15.6)	62 (8.6)
Nausea and vomiting (n, %)	1364 (11.6)	987 (12.1)	311 (11.1)	66 (9.2)
Headache (n, %)	1234 (10.5)	932 (11.4)	245 (8.7)	57 (7.9)
Irritability (n, %)	838 (7.2)	556 (6.8)	243 (8.6)	39 (5.4)
Throat pain (n, %)	700 (6.0)	520 (6.3)	141 (5.0)	39 (5.4)
Anosmia (n, %)	424 (3.6)	334 (4.1)	79 (2.8)	11 (1.5)
Missing (n, %)	*855 (7.3)*	*593 (7.2)*	*216 (7.7)*	*46 (6.4)*
Runny nose (n, %)	416 (3.6)	301 (3.7)	91 (3.2)	24 (3.3)
Clinical signs at admission	9993 (85.3)	7005 (85.5)	2452 (87.3)	536 (74.7)
Abnormal pulmonary imaging (n, %)*	7396 (63.1)	5271 (64.4)	1835 (65.3)	290 (40.4)
Abnormal pulmonary auscultation (n, %)	5245 (44.8)	3701 (45.2)	1343 (47.8)	201 (28.0)
Dyspnea (n, %)	4966 (42.4)	3462 (42.3)	1196 (42.6)	308 (42.9)
Pharyngitis (n, %)	244 (2.1)	174 (2.1)	58 (2.1)	12 (1.7)
Coma (n, %)	72 (0.6)	50 (0.6)	16 (0.6)	6 (0.8)
Conjunctivitis (n, %)	57 (0.5)	37 (0.5)	18 (0.6)	2 (0.3)
Convulsions (n, %)	15 (0.1)	12 (0.1)	3 (0.1)	0 (0.0)

ACEI; Angiotensin converting enzyme inhibitors, ARBs. Angiotensin receptor blockers
** Reported as abnormal pulmonary imaging compatible with pneumonia*

Table 2 Supplemental. Results (OR, 95%CI) of variable selection models of conditions associated with ACEI/ARBs use among factors with COVID-19 prognosis[1]

Variable	Model 1	*p*-value	Model 2	*p*-value
Intercept	0.04 (0.03-0.05)	< 0.0001	0.03 (0.03-0.05)	< 0.001
Gender (male)	1.33 (1.21-1.47)	< 0.0001	1.26 (1.12-1.41)	< 0.001
Age	1.01 (1.01-1.02)	< 0.0001	1.01 (1.01-1.02)	< 0.001
CVD	1.71 (1.55-1.90)	< 0.0001	1.65 (1.46-1.87)	< 0.001
Diabetes	1.38 (1.24-1.54)	< 0.0001	1.37 (1.20-1.56)	< 0.001
HBP	5.65 (5.10-6.27)	< 0.0001	5.28 (4.66-6.00)	< 0.001
Obesity			1.33 (1.10-1.59)	< 0.01
Cognitive impairment			0.69 (0.58-0.82)	< 0.001

[1] *Backwards stepwise logistic regression with variable selection according to AIC; OR, odds ratio. Model 1 included: Gender, age, HBP, CVD, DM, chronic renal disease, chronic liver disease, chronic lung disease, solid malignant neoplasms, hematological cancers, immunodepression (N=10866); Model 2 included: Model 1 variables plus cognitive impairment, chronic neuro-muscular disease, and obesity, for which a high degree of missingness was observed and represents a complete case analysis (N=7,294)*

Table 3 Supplemental. State-arrival extended Cox-Markov models transitions hazard ratios (HR, 95%CI) as a function of ACEI/ARBs and identified confounders

Model 1

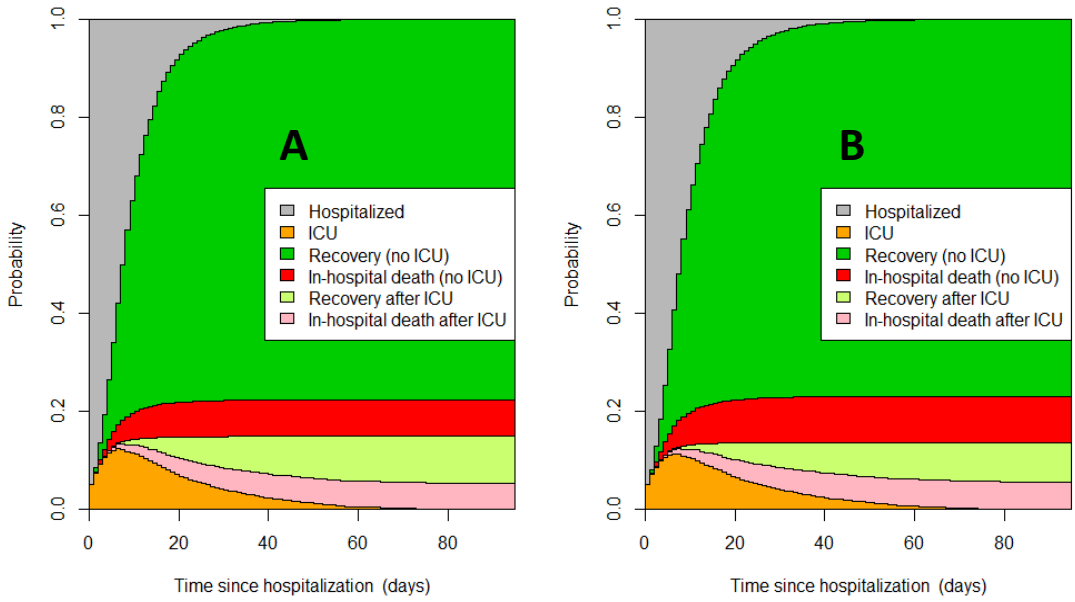
Transition		ACEI/ARBs use	Male gender	Age < 70	Age > 70	CVD	HBP	DM	Time to severity
1	Admission to Severity	1.15 (0.98, 1.36)	**1.83 (1.58, 2.12)**	**1.02 (1.01, 1.02)**	**0.90 (0.89, 0.91)**	0.96 (0.82, 1.12)	**1.35 (1.15, 1.58)**	0.94 (0.79, 1.11)	
		0.092	<0.0001	<0.0001	<0.0001	0.575	<0.0001	0.440	
2	Admission to Recovery	**1.07 (1.01, 1.13)**	**0.89 (0.85, 0.93)**	**0.97 (0.97, 0.97)**	**0.96 (0.96, 0.97)**	**0.86 (0.81, 0.91)**	**0.95 (0.89, 1.00)**	**0.92 (0.87, 0.98)**	
		0.027	<0.0001	<0.0001	<0.0001	<0.0001	0.043	0.007	
3	Admission to Death	**0.83 (0.75, 0.93)**	**1.45 (1.31, 1.59)**	**1.11 (1.09, 1.13)**	**1.05 (1.04, 1.05)**	**1.13 (1.02, 1.25)**	1.00 (0.90, 1.10)	1.09 (0.98, 1.22)	
		0.001	<0.0001	<0.0001	<0.0001	0.015	0.947	0.102	
4	Severity to recovery	1.16 (0.97, 1.38)	0.90 (0.77, 1.04)	**0.97 (0.96, 0.97)**	1.00 (0.98, 1.02)	1.03 (0.87, 1.21)	0.95 (0.81, 1.12)	1.01 (0.85, 1.19)	**0.95 (0.93, 0.97)**
		0.098	0.158	<0.0001	0.799	0.766	0.570	0.919	<0.0001
5	Severity to death	0.91 (0.73, 1.13)	1.11 (0.91, 1.36)	**1.05 (1.03, 1.06)**	1.05 (1.03, 1.07)	1.07 (0.88, 1.30)	0.90 (0.74, 1.11)	**1.25 (1.02, 1.53)**	1.02 (1.00, 1.04)
		0.381	0.316	<0.0001	<0.0001	0.494	0.326	0.034	0.056

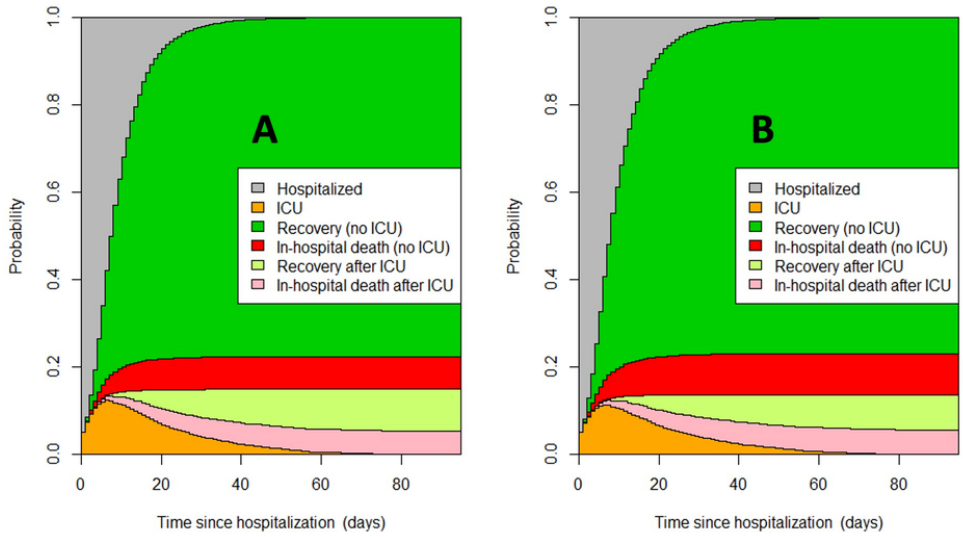
Model 2

Transition		ACEI/ARBs use	Male gender	Age < 70	Age > 70	CVD	HBP	DM	Cognitive issues	Obesity	Time to severity
1	Admission to severity	1.10 (0.88, 1.36)	**1.71 (1.42, 2.08)**	**1.02 (1.01, 1.03)**	**0.92 (0.90, 0.93)**	0.91 (0.74, 1.12)	**1.45 (1.18, 1.79)**	0.96 (0.77, 1.19)	**0.52 (0.35, 0.77)**	**1.58 (1.24, 2.02)**	
		0.409	<0.0001	0.001	<0.0001	0.361	0.001	0.686	0.001	<0.0001	
2	Admission to recovery	1.05 (0.98, 1.13)	**0.89 (0.84, 0.94)**	**0.97 (0.97, 0.97)**	**0.97 (0.96, 0.97)**	**0.88 (0,82, 0.94)**	0.97 (0.91, 1.04)	0.93 (0.87, 1.00)	**0.83 (0.76, 0.91)**	1.01 (0.92, 1.11)	
		0.182	<0.0001	<0.0001	<0.0001	<0.0001	0.377	0.061	<0.0001	0.882	
3	Admission to death	**0.80 (0.70, 0.91)**	**1.48 (1.31, 1.66)**	**1.10 (1.07, 1.12)**	**1.05 (1.04, 1.05)**	**1.13 (1.00, 1.27)**	1.03 (0.91, 1.16)	1.11 (0.97, 1.27)	**1.36 (1.19, 1.55)**	0.97 (0.76, 1.24)	
		0.001	<0.0001	<0.0001	<0.0001	0.048	0.685	0.116	<0.0001	0.824	
4	Severity to recovery	1.16 (0.93, 1.45)	0.90 (0.75, 1.09)	**0.97 (0.96, 0.98)**	1.00 (0.97, 1.02)	1.12 (0.91, 1.38)	1.00 (0.81, 1.24)	0.95 (0.77, 1.16)	1.22 (0.84, 1.77)	0.97 (0.77, 1.22)	**0.94 (0.91, 0.97)**
		0.195	0.272	<0.0001	0.861	0.288	0.984	0.597	0.297	0.781	<0.0001
5	Severity to death	1.11 (0.83, 1.49)	1.22 (0.93, 1.60)	**1.04 (1.02, 1.06)**	**1.06 (1.03, 1.08)**	1.08 (0.82, 1.41)	0.81 (0.61, 1.08)	**1.44 (1.10, 1.90)**	0.89 (0.53, 1.50)	0.97 (0.69, 1.36)	**1.04 (1.01, 1.06)**
		0.485	0.146	<0.0001	<0.0001	0.591	0.150	0.008	0.668	0.860	0.003

ACEI/ARBs, Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers; CVD, cardiovascular disease; DM, diabetes mellitus; HBP, high blood pressure. Model 1: Adjusted for gender, age (years), CVD, HBP, DM, and time (days) to severity; Model 2: Further by prevalent obesity, and cognitive issues.

Figure 1 Supplemental.





Staked probability plot of the state-occupation probabilities in a multi-state competing risk model considering ACEI/ARBs use (A) versus no use (B).

40x24mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	8-10
Study size	10	Explain how the study size was arrived at	6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-10
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, and Fig 1
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	11, Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11, Table 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-11, *table 2*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 table 3
		(*b*) Report category boundaries when continuous variables were categorized	All tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13, Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.